FORMULATION DEVELOPMENT AND EVALUATION OF FLOATING MICROBALOONS OF ZIPRASIDONE HYDROCHLORIDE

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THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment for the award of the degree of

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IN

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Submitted by

Register Number: 26111010

UNDER THE GUIDANCE OF

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DECLARATION

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ABBREVIATIONS

API	Active Pharmaceutical Ingredient
CDDS	Controlled Drug Delivery Systems
CI	Compressibility Index
CRDF	Controlled Release Dosage Forms
DMSO	Dimethylsulphoxide
DNA	Deoxy Ribo nucleic acid
DOE	Design Of Experiments
EC	Ethyl Cellulose
FDDS	Floating Drug Delivery Systems
FTIR	Fourier Transformer Infrared Spectroscopy
GIT	Gastro Intestinal Tract
GRDF	Gastro Retentive Dosage Form
GRT	Gastric Retention Time
HBS	Hydrodynamically Balanced system
HCL	Hydrochloric Acid
HPMC	Hydroxy Propyl Methyl Cellulose
HR	Hausner Ratio
IP	Indian Pharmacopoeia
IPA	Isopropyl Alcohol
MMC	Migrating Mylo Electricitycycle
PVA	Poly Vinyl Alcohol
RH	Relative Humidity
USP	United States Pharmacopoeia
WHO	World Health Organisation

NOMENCLATURE

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Ng	Nanogram
ng/ml	Nanogram/millilitre
ng-hr/ml	Nanogram-hour/millilitre
Sec	Seconds

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1. INTRODUCTION

1.1 Oral Controlled Drug Delivery System: [1]

Oral controlled release dosage forms (CRDF) have been extensively used to improve therapy of many important medications. The design of oral controlled drug delivery systems (CDDS) should primarily be aimed at achieving more predictable and increased bioavailability of drugs.

However, the developmental process is precluded by several physiological difficulties, such as inability to restrain and locate the CDDS within desired regions of gastrointestinal tract (GIT) due to the variable gastric emptying and motility.

The variability may lead to unpredictable time for peak plasma levels and bioavailability. Therefore, the CRDF approaches has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the GIT, i.e. stomach and small intestine, which is due to relatively short transit time of the dosage form in these anatomical segments.

Thus within a short period (less than 6 hours), the CRDF of such drugs leave the upper part of GIT and reaches to the non-absorbing distal segment, eventually resulting in a short absorption phase accompanied with lesser bioavailability.

Invariably, conventional dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time. To achieve the same, a drug may be administered repeatedly using a fixed dosing interval. This causes several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve in Figure 1

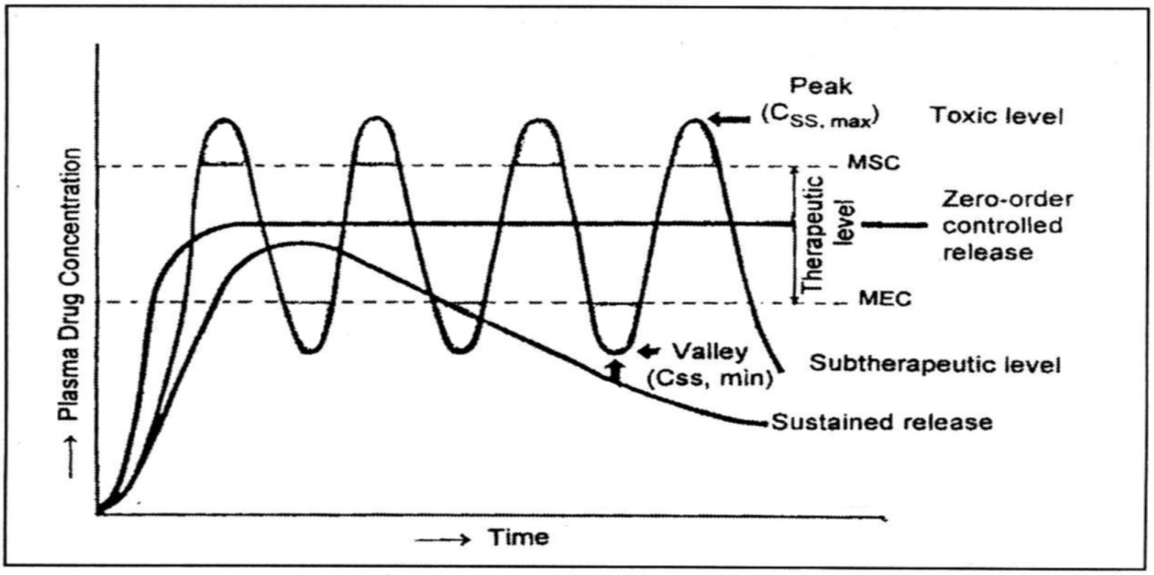


Figure 1: Plasma level profiles following conventional and controlled release dosing

The relatively brief gastric emptying time in humans normally averages 2 to 3 hours. through the major absorption zone (stomach or upper part of the intestine), which can result in incomplete drug release from the drug delivery system leading to diminished efficacy of the administered dose.

Thus, placement of the drug delivery system in a specific region of the GIT offers numerous advantages, especially to the drugs having narrow absorption window in GIT, primary absorption in the stomach, stability problem in intestine, poor solubility at alkaline pH, local activity in stomach and property to degrade in colon. Compounding the drugs with narrow absorption window in a unique pharmaceutical dosage form, which prolongs the gastric residence time would enable an extended absorption phase of these drugs.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the GIT is to control the gastric residence time, using gastro-retentive dosage forms (GRDF). GRDF are the drug delivery systems that are designed to be retained in the stomach for a prolonged time and release their active materials and thereby enable sustained input of the drug to the upper part of the GIT.

This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important

drugs for which prolonged retention in the upper GIT can greatly improve their oral bioavailability and/or their therapeutic outcome in Figure 2

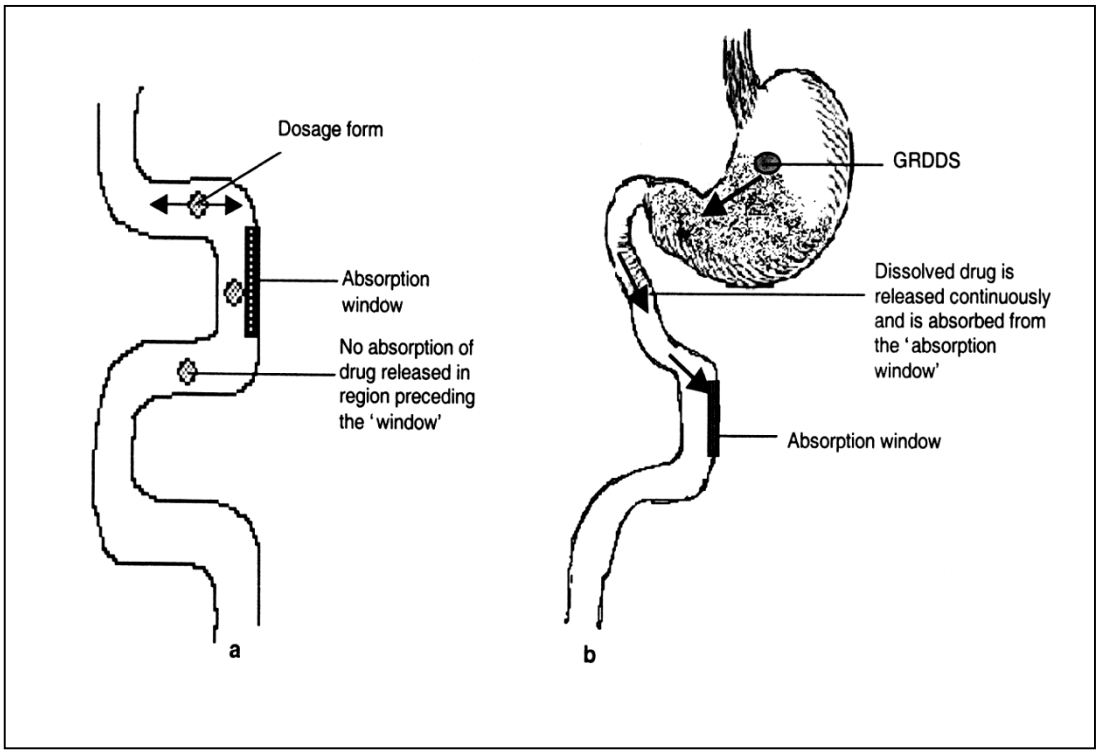


Figure 2:Comparison of conventional dosage form and gastro retentive dosage form

In the last three decades various attempts have been made to develop a novel and efficient gastro-retentive dosage forms which can retain in the stomach for an extended period of time in a predetermined manner.

This can be achieved by improving scientific and technological advancement to overcome physiological problems like pH of the stomach, motility and gastric emptying time by altering physiological and formulation variables. Many approaches are utilized in the development of gastric retention drug delivery systems viz., floating systems, swelling, expanding, high density, super porous hydrogels, bioadhesive, modified shape systems, ion exchange resin and by the simultaneous administration of pharmacological agents that delay gastric emptying. By utilizing one of these techniques it is possible to deliver drugs that have narrow absorption window.

From the formulation and technological point of view, the floating drug delivery system (FDDS) is considerably easy and logical approach in the development of

GRDF. Floating drug delivery system float on the gastric fluid only when it has density less than that of gastric fluids, i.e. <1g/cm^3. Usually, floating formulations are prepared from hydrophilic matrices that either have a density lower than one or their density drops below one after immersion in the gastric fluids owing to swelling.

More sophisticated devices are developed later and involved the use of various film coating techniques, incorporation of a floating chamber that is filled with harmless gas, or a liquid that gasifies at body temperature.

These systems are often called hydro-dynamically balanced system as they can maintain low density and keep floating even after hydrating. This system provides several advantages as prolonged gastric retention of drugs, improves bioavailability, reduces drug wastage and improves solubility for drugs that are less soluble in alkaline pH environment and provides local drug delivery to the stomach and proximal small intestine.

1.2 Basic physiology of stomach[2]:

The stomach is a 'J' shaped enlargement of the GI tract directly inferior to the diaphragm in the epigastric, umbilical and left hypochondria regions of the abdomen. The stomach connects the esophagus to the duodenum, the first part of the small intestine. Anatomy of stomach is shown in Figure 3.

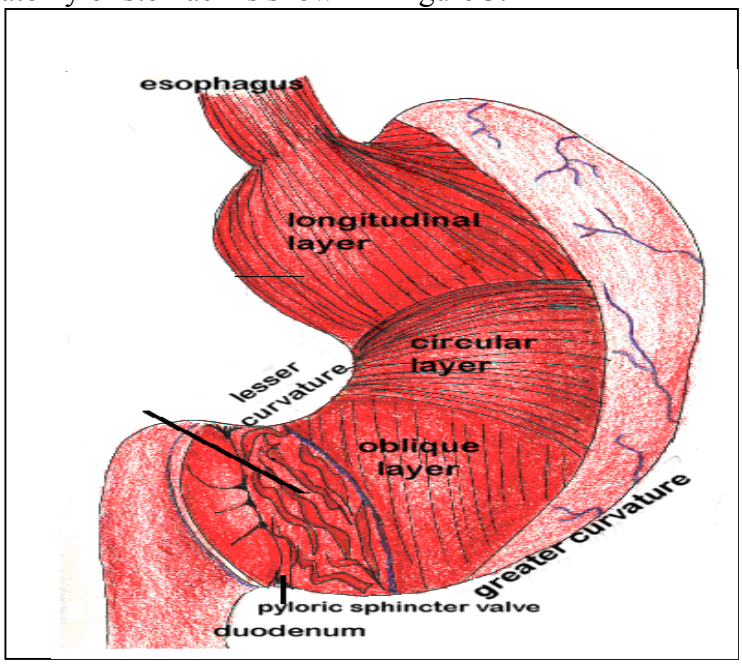


Figure 3: Anatomy of stomach

The stomach lies between the esophagus (proximally) and the duodenum (distally). It varies widely in size and shape depending on the person, the food content, and the posture of the body. It is J-shaped normally and the pyloric part lies horizontally or ascends to meet the proximal part of the duodenum.

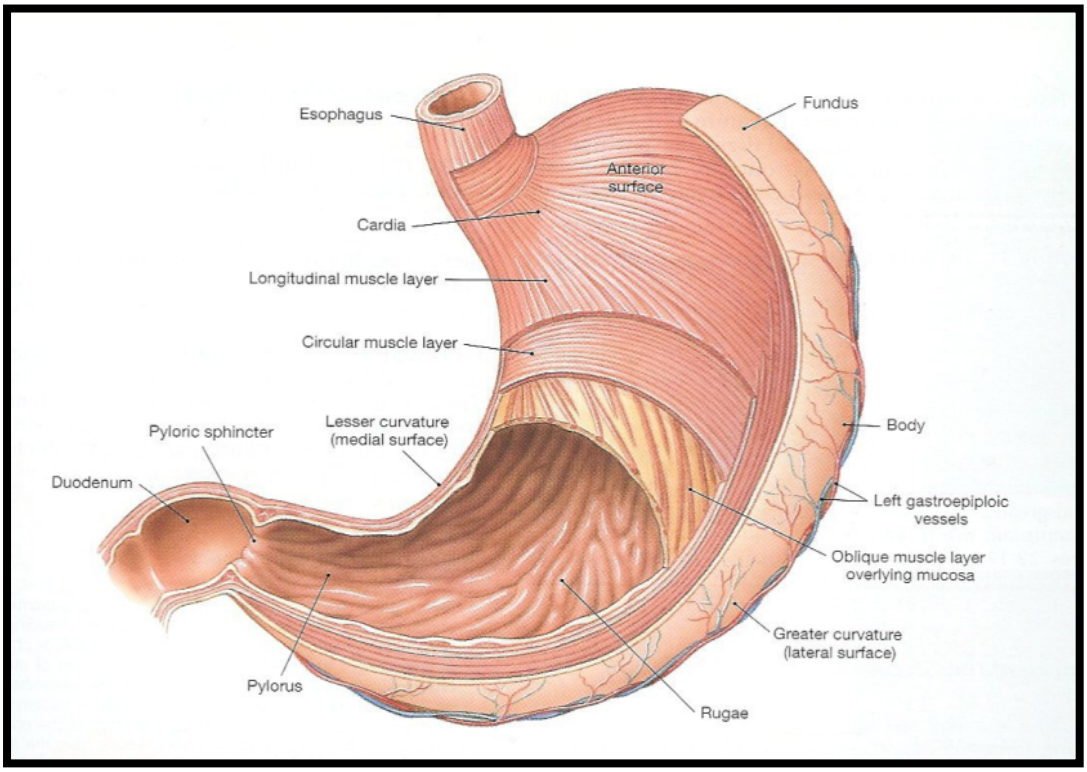


Figure 4: Structure of the stomach

Anatomically the stomach is divided into 3 regions:

- **Fundus**: The superior part of the stomach, this lies above the imaginary horizontal plane passing through the cardiac orifice.
- **Body**: This lies between the fundus and the antrum, and it is the largest part of the stomach.
- **Antrum**: This lies in the imaginary transpyloric plane and to the right of the angular notch. It joins the pyloric canal on its right.

The main function of fundus and body is storage whereas that of antrum is mixing or grinding. The fundus adjusts to the increased volume during eating by

relaxation of the fundus muscle fibers. The fundus also exerts a steady pressure on the gastric contents, pressing them towards the distal stomach. To pass through the pyloric valve into the small intestine, particles should be of the order of 1 to 2 mm. The antrum does this grinding. The stomach has limitation of short residence time.

1.3 Gastric Motility[3]:

The pattern of motility is distinct in fasted and fed states. During the fasting state an inter digestive series of electrical events takes place, which cycle both through stomach and intestine every 2 to 3 hrs. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle, which is divided into following 4 phases.

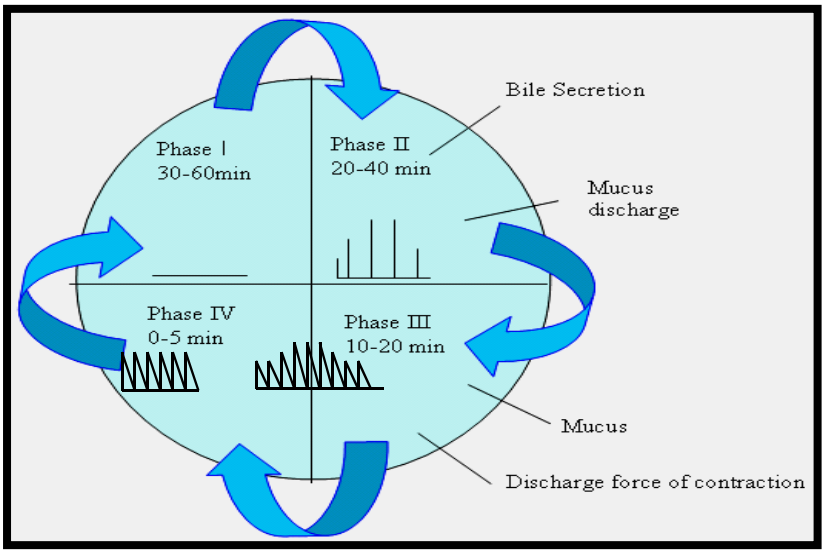


Figure 5: Motility Patterns of the GIT in the Fasted State

- **Phase I (basal):**

Lasts for 30 to 60 minutes. With rare contractions and is characterized by a lack of secretary, electrical, and contractile activity.

- **Phase II (preburst):**

Lasts for 20 to 40 minutes. with intermittent action potential and contractions.

- **Phase III (burst):**

  Lasts for 10 to 20 minutes. Includes intense and regular contractions. It is due to this wave that all undigested material is swept out of the stomach down to the small intestine. It is also known as housekeeper wave.

- **Phase IV:**

  Lasts for 0 to 5 minutes.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to fed state. It comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (<1mm), which are propelled towards pylorus. During fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

1.4 Gastric Emptying[1,3]:

It can be anticipated that, depending upon the physiological state of subject and design of pharmaceutical formulation, the emptying process last from a few minute to 12 hours.

Furthermore the relatively brief gastric emptying time in humans which normally averages 2 to 3 hours through the major absorption zone (stomach or upper part of intestine). Particle size and feeding state strongly affect the residence time of particles in the stomach.

Some other factors affecting gastric emptying are type of meal and its caloric content, volume, viscosity and co-administered drugs. The rate of gastric emptying primarily depends on the caloric contents of the ingested meal. It does not differ for proteins, fats, and carbohydrates as long as their caloric content is the same. Generally an increase in acidity, osmolarity and caloric value slows down gastric emptying.

Stress increases gastric emptying rate whereas depression slows it down. Females have a slower gastric emptying rate than males. Age and obesity also affect

gastric emptying. Gastric emptying of dosage forms is different in fasted and fed conditions.

Table 1: Transit time of various dosage forms across the segments of the Gastro Intestinal Tract

Dosage forms	Transit time (hours)		
	Stomach	Small intestine	Total
Tablets	2.7	3.1	5.8
Pellets	1.2	3.4	4.6
Capsules	0.8	3.2	4.0
Solution	0.3	4.1	4.4

1.5 Factors affecting gastric emptying time[4]:

1.5.1 Volume:

The resting volume of stomach is about 25 to 52 ml. This volume is important for dissolution of dosage forms. As the volume is large, emptying is faster. Gastric emptying of small volumes like 100 ml or less is governed by MMC cycle whereas large volumes of liquids like 200 ml or more are emptied out immediately after administration. Fluids at body temperature leave the stomach more rapidly than either warmer or colder fluids.

1.5.2 Hormonal Effects:

Stress conditions increases gastric emptying rate whereas depression slows down gastric emptying time. Generally females have slower gastric emptying rate than males. Age and obesity also affect gastric emptying.

1.5.3 Presence of Food:

Gastric emptying time differs in fasted state and in fed state. The caloric value of food affects the gastric emptying time.

1.5.4 Gastric Secretions:

Acids, pepsin, gastrin, mucus and other enzymes are the secretions of stomach. Normal adults produce a basal secretion upto 60 ml with approximately 4 millimoles of hydrogen ions every hour.

1.6. Factors affecting gastric residence time of dosage form[5]

1.6.1 Density:

Gastric residence time increases if the density of the dosage form is less than the gastric contents (<1.004 gm/ml).

1.6.2 Size and Shape:

Small-size tablets leave the stomach during the digestive phase while the large size tablets are emptied during the housekeeping waves.

1.6.3 Fed or Unfed state:

Under fasting conditions, the GI motility is characterized by periods of MMC that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the gastric residence time of the unit can be expected to be very short. However, in the fed state, MMC is delayed and gastric residence time is considerably longer.

1.6.4 Frequency of Feed:

The gastric residence time can be increased by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

1.6.5 Posture:

Gastric residence time can vary between supine and upright ambulatory state of the patients.

1.6.6 Concomitant drug administration:

Anticholinergics like atropine and propentheline, opioids like codeine and prokinetic agents like metoclopromide and cisapride affects the GRT when administered together.

1.6.7 Biological Factors:

Diabetes and Crohn's disease also affects gastric residence time.

1.7.Formulation approaches for gastro retentive drug delivery systems (GRDDS)[6]

There are several formulation approaches used for designing GRDDS. These include Swelling and Expanding system, which are retained in the gastric region due to their large size gained after swelling.

Floating system are retained in the gastric region due to their floating ability on the gastric fluid. The floating system is further divided into single unit system such as floating tablets and multiparticulate systems such as floating microspheres, which offer more advantages as compared to single unit system.

The floating system is further divided into effervescent and non-effervescent floating system based on their mechanism of floating. Bioadhesive systems adhere to the gastric mucosa due to which they are retained in the gastric region.

High density system are retained due to their increased density then the gastric fluid. Beside this, passage delaying food as well as drugs can be administered simultaneously to retain the dosage form in the gastric region.

The Flowchart shows the various approaches used to retain the dosage forms in the gastric region.

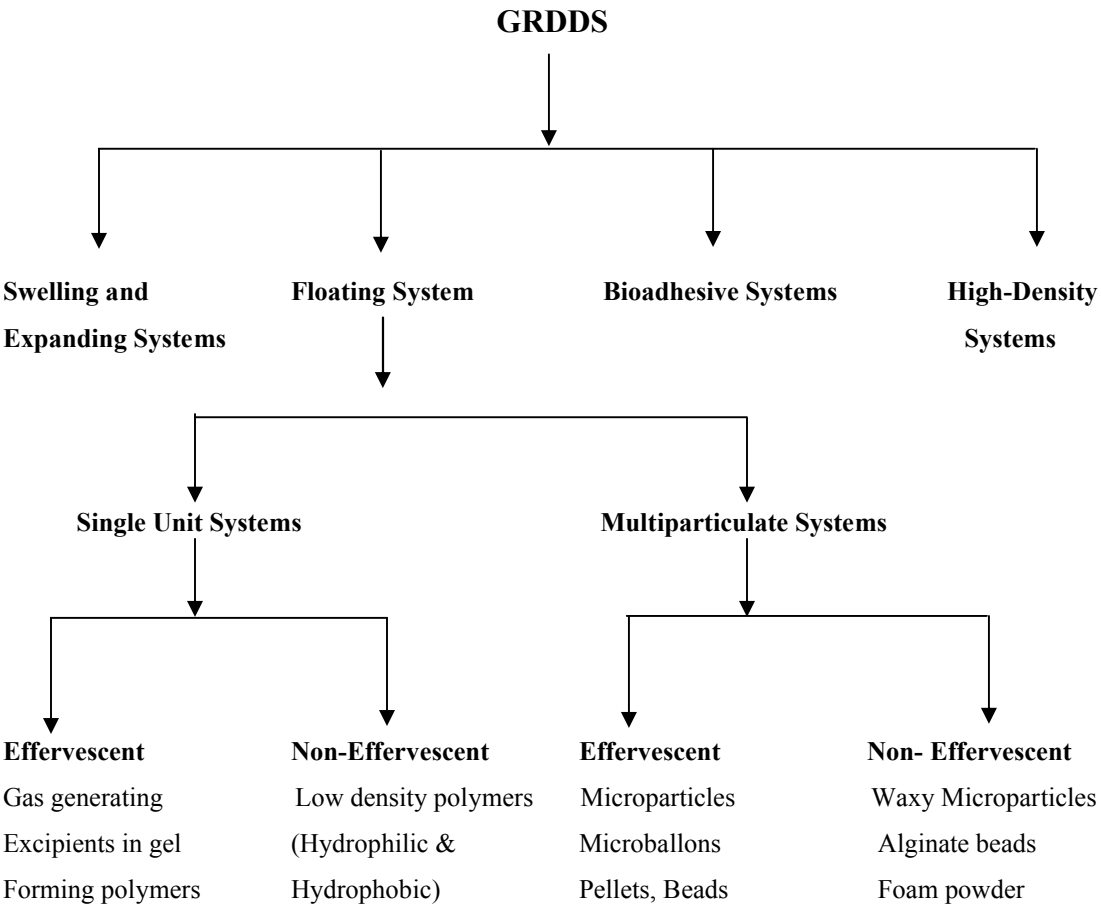


Figure 6: Flowchart enlisting various approaches used for designing FDDS

1.7.1 Swelling and Expanding systems:

Swelling type dosage forms are such that after swallowing, these products swell to an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as 'plug type' systems since they exhibit tendency to remain lodged at the pyloric sphincter.

1.7.2 Floating System (Low Density Approach):

These systems are also known as hydro-dynamically balanced systems. (HBS/FDDS) They have a bulk density lower than gastric fluid, i.e. their bulk density is less than one. The specific gravity of gastric fluid is approximately 1.004 to 1.010 g/cm^3 and thus the FDDS remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at a desired rate from the system. After the release of the drug the residual system is emptied from the stomach.

1.7.3 Bioadhesive Systems:

They are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. It makes use of bioadhesive polymers. These polymers tend to form hydrogen and electrostatic bonds at the mucus polymer boundary.

1.7.4 High Density Systems:

High density formulations include coated pellets that have density greater than that of stomach contents. ($>1.004 g/cm^3$) This is accomplished by coating the drug with heavy inert materials such as Barium sulfate, Titanium dioxide, Iron powder or oxide. The weighted pellet can then be covered with a diffusion-controlling polymer membrane.

1.7.5.Modified Shape Systems:

These are non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends which extend the gastric residence time depending on size and shape of the dosage form

1.7.6.Use of other delayed gastric emptying devices:

It includes feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release.

1.7.7.Osmotic regulated system:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components are as: drug reservoir compartment and osmotically active compartment.

Incorporation of passage delaying food agents:

The food excipients like fatty acids, e.g. salts of Myrestic acid change and modify the pattern of the stomach to a fed state, there by decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10} to C_{14}.

1.7.8.Ion exchange resin:

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin, resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach and exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in a membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast the uncoated beads, which will sink quickly.

1.8.Design and fabrication of Floating drug delivery system (FDDS)[4,5]

1.8.1 Non - Effervescent FDDS

1.8.1.1 Colloidal gel barrier system:

HBS of this type contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. They help prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption.

These systems incorporate high levels (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids e.g. Hydroxyl Ethyl Cellulose, Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose, Sodium Carboxy Methyl Cellulose, Polysaccharides and matrix forming polymers such as Polycarbophil, Polyacrylates and polystyrene incorporated either in tablets or capsules.

When such a system comes in contact with the gastric fluid, the hydrochloride in the system hydrates and forms a colloidal gel barrier around its surface. The air trapped inside the swollen polymer maintains the density less than unity and confers buoyancy to these dosage forms. This gel barrier controls the rate of the fluid penetration into the device and consequent release of drug from it.

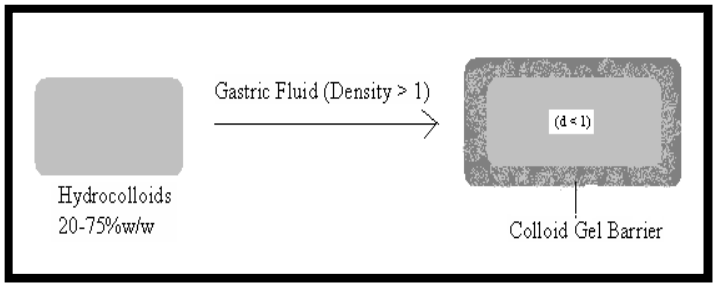


Figure 7: Colloidal gel barrier floating tablet

The HBS must comply with following three major criteria:

- It must have sufficient structure to form cohesive gel barrier.
- It must maintain specific density lower than that of gastric contents.
- It should dissolve slowly to serve as reservoir for the delivery system.

A bilayer tablet can also be prepared to contain one immediate release and other sustained release layer. Immediate release layer delivers the initial dose whereas sustained release layer absorbs gastric fluid and forms a colloidal gel barrier on its surface. This results in system with bulk density lesser than that of gastric fluid and allows it to remain buoyant in the stomach for an extended period of time.

A multi-layer, sheath-like device buoyant in gastric juice showing sustained release characteristics has also been developed. The device consists of at least one dry self-supporting carrier film made up of water insoluble polymer matrix having a drug dispersed/dissolved therein, and a barrier film overlaying the carrier film. Both carrier and barrier films are sealed together along their periphery and in such a way as to entrap a plurality of small air pockets, which bring about the buoyancy to the laminated films.

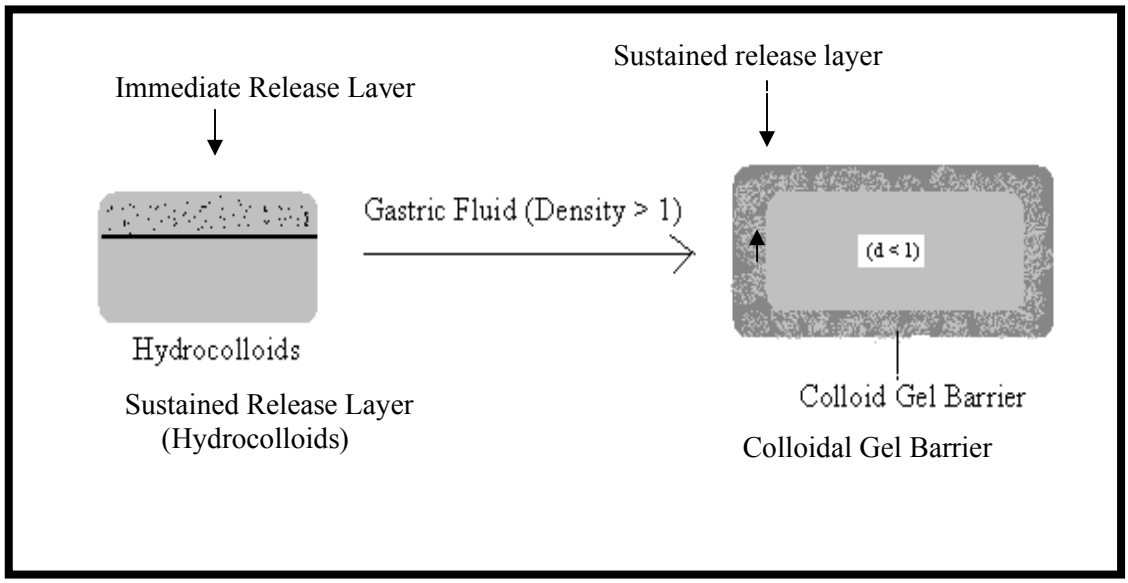


Figure 8: Bilayer intra-gastric Floating tablet

1.8.1.2 Micro-porous compartment system:

This technology is comprised of encapsulation of a drug reservoir inside a micro-porous compartment with pores along its top and bottom surfaces. The

peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with undissolved drug.

In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

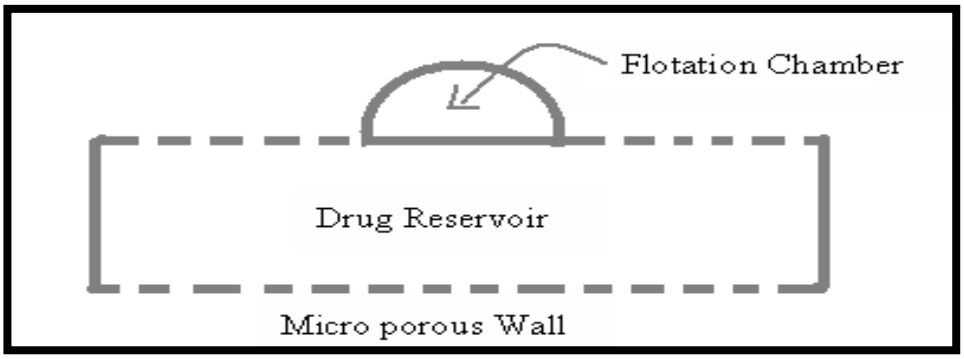


Figure 9: Micro-porous intra-gastric FDDS

1.8.1.3 Alginate beads:

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter were prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing a precipitation of calcium alginate. These beads were then separated, snap frozen in liquid nitrogen and freeze-dried at 40^0C for 24 hours, leading to formation of porous system that maintained floating force for over 12 hours. They were compared with non-floating solid beads of same material. The latter gave a short residence time of 1 hour, while floating beads gave a prolonged residence time of more than 5.5 hours.

Floating systems comprising of calcium alginate core separated by an air compartment from a membrane of calcium alginate or a calcium alginate/polyvinyl alcohol (PVA) have also been developed. The porous structure generated by leaching of PVA (water soluble additive in coating composition) was found to increase membrane permeability and thus preventing the collapse of air compartment.

1.8.1.4 Hollow Microspheres:

Hollow microspheres (micro-balloons) loaded with Ibuprofen in their outer polymer shells were prepared by novel emulsion solvent diffusion method. The Ethanol:Dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 40^{o} C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in microsphere of polymer with drug. These micro-balloons floated continuously over surface of acidic solution media that contained surfactant, for greater than 12 hours *In-vitro*. The drug release was high in pH 7.2 than in pH 6.8.

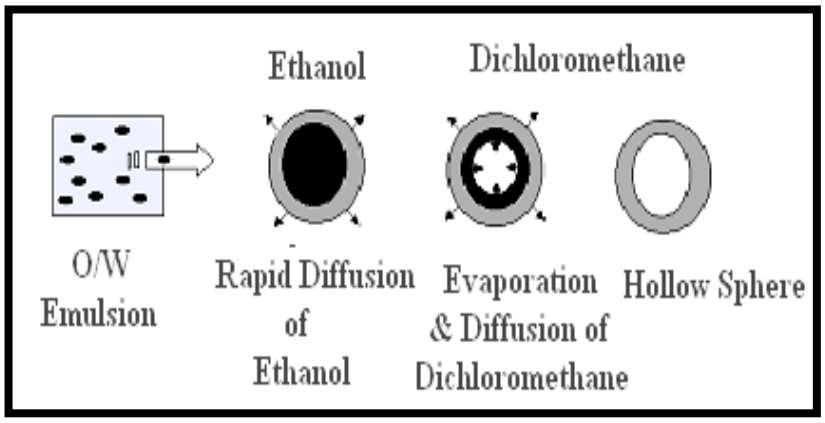


Figure 10:Diffusion method-Mechanism of Micro-Balloon formation by Emulsion-solvent

1.8.1 Effervescent systems:

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts.

1.8.2.1 Volatile Liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber which contains a liquid e.g. Ether or Cyclo-pentane that gasifies at body temperature to cause the inflation of the chamber in the stomach. These devices are osmotically controlled floating systems containing a hollow

deformable unit that can be converted from a collapsed to an expanded position and returned to collapsed position after an extended period. A deformable system consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber contains volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach**.**

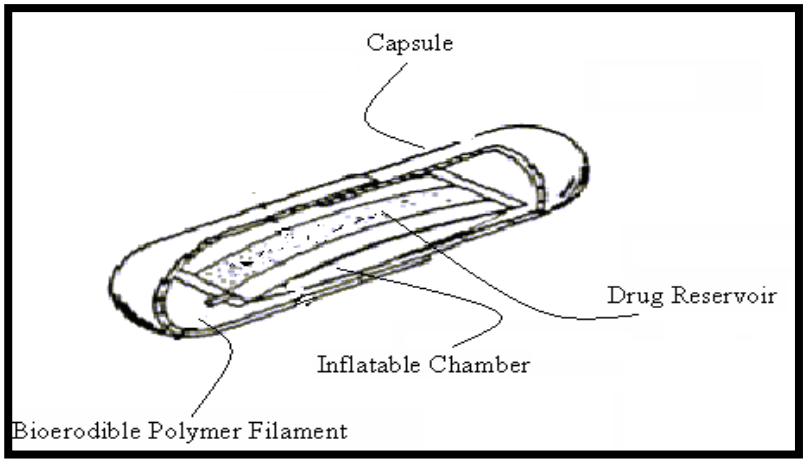


Figure 11: Gastro inflatable drug delivery device

Intra-gastric, osmotically controlled drug delivery system consists of an osmotic pressure controlled drug delivery device and an inflatable floating support in bioerodible capsule.

When the device reaches the stomach, bioerodible capsule quickly disintegrates to release the drug delivery system. The floating support is made up of a deformable hollow polymeric bag containing a liquid that gasifies at body temperature to inflate the bag.

The osmotic pressure controlled part consists of two compartments, a drug reservoir compartment, and an osmotically active agent-containing compartment. The

drug reservoir compartment is enclosed in a pressure responsive collapsible bag, which is impermeable to vapors and liquid, and has a drug delivery orifice.

The osmotic compartment contains an osmotically active salt, and is enclosed within semi-permeable housing. In stomach, water is absorbed through the semi-permeable membrane into the osmotic compartment to dissolve the salt.

An osmotic pressure thus created acts on collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and release the drug solution through the delivery orifice. The floating support also contains a bioerodible plug that erodes after a predetermined time to deflate the support, which is then excreted from the stomach**.**

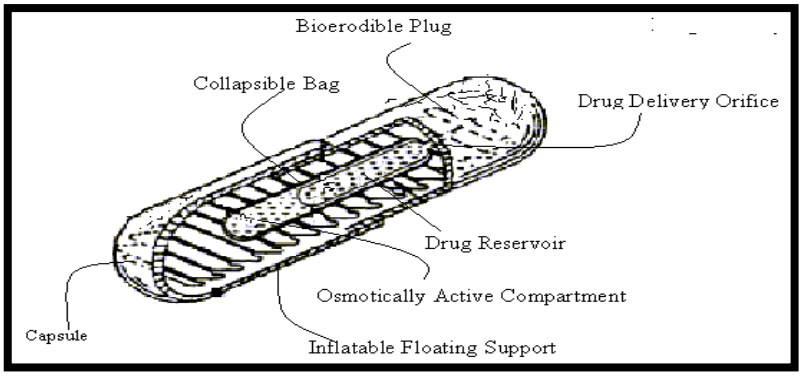


Figure 12: Intragastric osmotic controlled drug delivery system

1.8.2.2 Gas generating systems:

These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate Carbon-di-oxide which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity and making it float over chyme. Multiple unit type of floating pills that generate Carbon-di-oxide also has been developed. The system consists of sustained release pill as a seed, surrounded by double layer. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is swellable membrane layer. These kinds of systems float completely within 10 minutes and remain floating over an extended period of 6 to 24 hours

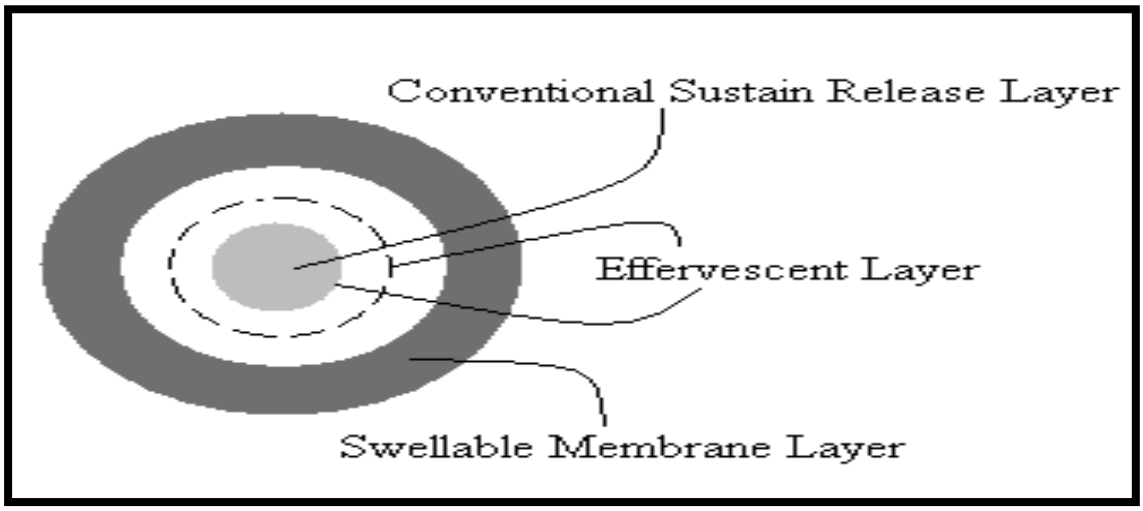


Figure 13:Multiple unit oral Floating dosage systems

Following figure shows mechanism of Floating of Effervescent drug delivery system:

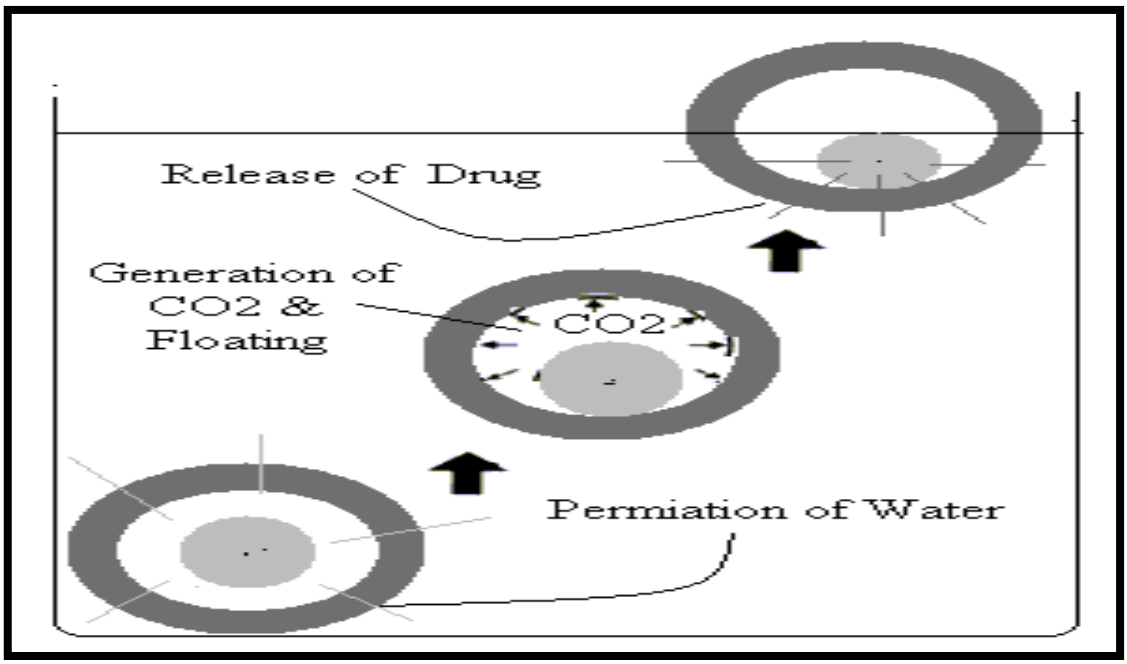


Figure 14: Mechanism of Effervescent drug delivery system

1.8.2 Recent advances in FDDS:

1.8.3.1 Floating multi-layer coated tablets:

Floating multi-layer coated tablets were designed based on gas formation. The system consists of a drug containing core tablet coated with a protective layer (Hydroxy propyl methyl cellulose), a gas forming layer (Sodium bicarbonate) and a gas-entrapped membrane, respectively. The acrylic polymers (Eudragit® RL 30D, RS 30D, NE 30D) and Ethylcellulose were suitable film for the system, and was chosen as a gas-entrapped membrane due to its high flexibility and high water permeability. The obtained tablets enabled to float due to the carbon-dioxide gas formation and the gas entrapment by polymeric membrane.

1.8.3.2 Raft system:

A gel–forming solution (e.g. Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped Carbon di-oxide bubbles on contact with gastric fluid. Formulations also typically contain antacids such as Aluminium hydroxide or Calcium carbonate to reduce gastric acidity. Because raft forming produce layer on the top of the gastric fluid, they are often used for gastro esophageal reflux treatment such as liquid gaviscon.

1.8.2.1 Magnetic system:

This system is based on a simple idea is that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of stomach.

The internal tablet guided by the oesophagus with an external magnet. These system seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

1.9. Criteria for selection of drug candidate for GRDF[6]:

- Drugs required to exert local therapeutic action in the stomach e.g. Misoprostol, 5-Flurouracil, Antacids and Anti-reflux preparations, Anti-helicobacter pylori agents and certain enzymes.

- Drugs exhibiting site-specific absorption in the stomach or upper part of the small intestine. e.g. Atenolol, Furosemide, Levodopa, p-Aminobenzoic acid, Piretanide and Salbutamol.
- Drugs unstable in lower part of GI tract. e.g. Captopril.
- Drugs insoluble in intestinal fluids (Acid soluble basic drugs). e.g. Chlordiazepoxide, Chlorpheniramine, Cinnarizine, Dizapam, Diltiazem, Metoprolol, Propranolol and Verapamil
- Drugs with variable bioavailability. e.g. Sotalol hydrochloride and Levodopa.

1.9.1.Advantages of FDDS[3,5]:

- It is advantageous for drugs absorbed through the stomach. for e.g. Riboflavin, Ferrous salts and Antacids.
- It is not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine.
- It is advantageous for drugs meant for local action in the stomach. for e.g. Antacids and Antiulcer drugs.
- The dissolved drug gets available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- It releases drug slowly and for prolonged period of time and hence reduces dosing frequency.
- It reduces fluctuations in circulating blood level of drug as shown by the conventional dosage form.
- It shows more uniform levels of drug in plasma.
- As it prolongs drug release it helps to avoid night time dosing.
- It reduces GIT irritation and other dose related side effects.
- It increases patient compliance as the dosing frequency is reduced.

1.9.2.Disadvantages of FDDS[3]

- The requirement of high levels of fluid in stomach for delivery system to float and work efficiently.
- These systems require the presence of food to delay their gastric emptying time.
- The drugs having solubility or stability problems in the highly acidic gastric environment or that are irritants to gastric mucosa are not good candidates for floating drug delivery system.
- In case of bioadhesive system which form electrostatic and hydrogen bond with mucus, the acidic environment and mucus prevent bond formation at mucus polymer interface.
- The dosage form designed to stay in stomach in the fasted state musts be capable of resisting the housekeeper waves of phase III of the MMC.
- The drugs which are well absorbed along the entire Gastro intestinal tract and which undergoes significant first pass metabolism, may not be desirable candidates for FDDS, since slow gastric emptying lead to reduced systemic bioavailability.

1.9.3.Marketed preparations of FDDS:[6]

Table 2: Marketed preparations of Floating drug delivery systems

S. No.	Product	Active ingredients
1	Madopar	Levodopa and Benserazide
2	Valrelease	Diazepam
3	Liquid Gavison	Alginic acid and bicarbonate
4	Conviron	Ferrous sulphate
5	Cifran OD	Ciprofloxacin
6	Cytochek	Misoprostol

REVIEW OF LITERATURE

1.Mona Semalty et al[7](2010) were attempted to Prepare and characterize gastroretentive floating microspheres of ofloxacinHcl using polymers ethyl cellulose, poly vinyl pyrrolidine K-90&poly vinyl alcohol in different ratios by solvent diffusion method. In *vitro* floatability studies revealed that most of the microspheres (52.5% to 95.5%) were floatable. The *in vitro* drug release was found to be in the range of 39.64 to 93.64% at the end of 6 hours.

2.Shankraiah M etal[8](2011) were attempted to formulate and evaluate floating microspheres of levofloxacin using polymers HPMC and Eudragit S100 in different ratios by emulsion solvent evaporation technique. The drug was encapsulated with HPMC and Eudragit S 100 in different polymers ratios. The % Yield of microspheres was high in HPMC batches over Eudragit S 100 batches. Percentage Buoyancy of microspheres was found to be in the range of 63.38%□75.58% indicated that most of the microspheres were still floatable after 12hours because of their low density and internal voids. Microspheres of levofloxacin with HPMC showed enhanced release rate when compared to Levofloxacin with Eudragit S 100.

3.P.Manisha et al[9](2010)were attempted to prepare and evalute the floating Microspheres of famotidine using hydroxylpropyl methylcellulose (HPMC) and Ethylcellulose (EC) as the rate controlling polymers by solvent evaporation (Oil-in-water emulsion) technique. Results showed that the polymer ratio and stirring speed affected the size, incorporation efficiency and drug release of microspheres (> 12 h), floating time (> 12 hr) and the best results were obtained at the ratio of HPMC:EC (1:6).

4.M.Najmuddin et al[10](2010)were attempted to Formulate and evalute the floating micro spheres of ketoprofen using HPMC and two different grades of ethylcellulose as polymer by solvent evaporation method . Formulaion F5 prepared with HPMC 5 cps and ethylcellulose 7-10 cps which exhibited excellent micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release 98.88% for a period of 12 hrs.

5.Alkesh T et al[11] (2011)formulated floating tablets of Acyclovir using gas forming agents like sodium bicarbonate and natural gums like Locust bean gum, Sodium alginate and Xanthan gum by effervescent technique. The results of in vitro release studies showed that optimized formulation F7 could sustain drug release (99.08%) for 16 hr and remain buoyant for 24 hr. F7 formulation fitted best for Korsemeyer –Peppas model and showed no significant change in physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 45 °C/75% RH for two months.

6.Muthusamy K et al[12] (2005) prepared and evaluated Lansoprazole floating micropellets. The floating micropellets were prepared by emulsion solvent diffusion technique. The prepared micropellets showed sustained release of Lansoprazole in gastric medium for more than 12 hours, thereby improving its oral bioavailability.

7.ElKamel AH et al[13] (2003)developed floating microparticles of Ketoprofen using Eudragit S & L as polymers and studied the gastric ulcerogenic effect of Ketoprofen floating microparticles with plain Ketoprofen. Ketoprofen loaded microparticleswerefound to be less ulcerogenic and they protected the stomach by preventing the intimate contact of Ketoprofen with gastric mucosa.

8.El-GibalyI et al[14] (2002)formulated and compared chitosan floating microcapsules containing Melatonin with conventional non-floating Chitosan microspheres. Floating microcapsules showed zero order release kinetics and more than 12 hrs floating time in vitro. Moreover, these floating microcapsules greatlyretarded the drug release lasting for several hours while it was almost instant fromconventional microspheres.

9.Basak SC et al[15] (2004)developed oral floating matrix tablet of Ciprofloxacin using gas generating agent sodium bicarbonate, and hydrophilic polymer Hydroxypropyl methyl cellulose. Drug release study of these tablets indicated

controlled sustained release of Ciprofloxacin, thereby improving its bioavailability.

10.Bhaskaran S et al(2004)developed hydrodynamic oral floating controlled delivery of Diltiazem hydrochloride as sustained release macropellets. Results revealed that the system had excellent floating ability and sustained release characteristics of zero order kinetics.

11.Baumgartner S etal[16](2000) developed floating matrix tablets containing Hydroxypropyl Methyl Cellulose, which after oral administration were designed to prolong the gastric residence time, increase bioavailability and diminish the side effects of irritating drugs. The importance of the composition optimization, formulation aspects and characterization of tablets were examined. The investigation showed that the tablet composition and mechanical strength have great influence on the floating and drug release properties of the tablets. They concluded that drug release from the tablets followed non-Fickian transport.

12.Joseph NJ et al[17] (2002)studied the effect of solvent evaporation technique on floating type hollow polycarbonate microsphere of Piroxicam which were capable of floating on simulated gastric fluid. Pharmacokinetic analysis showed that the bioavailability of Piroxicam hollow microsphere was about 1.4 times that of free drug and was about 4.3 times for the dosage form consisting of microsphere plus the loading dose. The elimination half life was increased by three times that of free drug.

13.Chandira M et al (2009) prepared floating tablets of Diltiazem Hydrochloride using direct compression technique using Hydrophilic polymer like HPMC K4M,HPMC K15M and hydrophobic polymer like Ethylcellulose as matrix materials in various quantities (%w/w), sodium bicarbonate, citric acid, magnesium stearate, talc and lactose in varying ratio to formulate the floating tablets. They observed that tablets of batch F6 followed the results obtained, it

was concluded that the formulation F6 is the best formulations as the extent of drug release was found to be around 99.81 % at the desired time 12 hrs.

14.Chandira M et al (2009)formulated floating tablets of famotidine using directly compression technique with polymers like HPMC K4M and HPMCK100M for theirgel-forming properties. They reported that gas powered gastroretentivefloatingTablets of famotidine containing 40mg HPMCK100M and Xanthan gum provides a better option for controlled release action and improved bioavailability.

15.Ozdemir N et al (2000)developed floating bilayer tablet of Furosemidecyclodextrin inclusion complex. They determined the gastric residence time using radiographs by adding BaSO4 and reported that the tablet stayed in stomach for 6 hours. Also the bioavailability of Furosemide from floating tablet was about 1.8 times those of the conventional tablet and also significant in vitro – in vivo correlation was detected.

16.Gohel MC et al[18] (2004) developed a more relevant in vitro dissolution method to evaluate Carbamazepine floating drug delivery system. The test showed good in vitro– in vivo correlation since the gastric volume, gastric emptying and gastric acid secretion rate were mimicked.

17.Kawashima Y et al[19] (1992) reported the formulation of hollow microspheres that floats in stomach. The hollow microspheres (microballons) loaded with either Tranilast or Ibuprofen in an outer enteric acrylic polymer (Eudragit S) shell and prepared by a novel emulsion-solvent diffusion method were studied for their physico-chemical properties, such as particle diameter, particle density and crystalline form of the drug. The microballoons floated continuously over the surface of acidic dissolution medium containing surfactant for 12 hours in vitro.

18.Shoufeng L et al (2001)developed an optimized gastric floating drug delivery system for oral controlled delivery of Calcium. A central, composite Box-Wilson design for the controlled release of calcium was used with three formulation variables; HPMC loading, citric acid loadingand magnesium stearate loading. All three formulation variables were found to significantly affect release properties. Only HPMC loading was found to be significant for floating properties.

19.Roughe N et al (1998) conducted a study to evaluate the factors that improves the in vitro buoyancy and drug release profile of floating minitablets containing either Piretinide or Atenolol as the model drug. The buoyancy of the minitablets was achieved either by the swelling of the excipients or by incorporating gas generating agent, sodium bicarbonate. The study concluded that it is possible to produce minitablets containing either Piretinide or Atenolol, which have a positive resultant weight during more than 6 hr and satisfactory release profiles.

20.Nath BS et al (1995) reported the development of wax and fat embedded microspheres of Ibuprofen as a drug delivery system. Paraffin, cetyl alcohol and stearic acid microspheres were prepared using methylcellulose, sodium alginate, and polysorbate 80 as emulsifying agents. Drug release was erosion controlled. The type of emulgent used influenced release kinetics. Retardation of drug release followed the order of stearic acid – methylcellulose, cetyl alcohol, polysorbate 80, and paraffinsodium alginate. Drug content was found to be uniform in all systems.

21.Maru AD et al[20] (1987)prepared intragastric floating controlled release tablets of Nitroglycerine and cimetidine. In vitro floating characteristics of nitroglycerine showed that the tablets continued to float on the surface of water for more than 24 hours which is the maximum duration during which the tablet is expected to release its total quantity of drug. Buoyancy of the formulation in vivo

was confirmed through endoscopy after administration of cimetidine floating tablets to the patients suffering from peptic ulcer.

22.Sangekar S et al[21] (1987)studied the effect of food and specific gravity on the gastric retention of floating and non-floating tablet formulations. The results obtained indicated that the presence of food in stomach appeared to prolong gastric retention significantly of both floating and non-floating tablet.

23.Hilton AK et al[22](1992)fabricated oral sustained release floating tablets of Amoxycillintrihydrate and carried out in vitro – in vivo evaluation. From the studies, it showed that the drug slowly released in the stomach by diffusion from the floating matrix tablet and then trickled towards the proximal intestine where absorption occurs. It improved the delivery of antibiotic resulting in more uniform levels of antibiotic following less frequent oral dosing.

24.Menon A et al[23] (1994) reported the formulation of a monolithic floating dosage form for Furosemide using factorial design keeping the drug to polymer ratio, polymer to polymer ratio and polymer grade as the three factors. The optimized formulation thus obtained was found to have a good in vitro / in vivo correlation.

25.Kohri N et al[24] (1996) revealed that gastric retained tablet of Sulpiride prepared from Carbopol 934P showed sustained release characteristics which was suitable forimproving and extending the oral bioavailability of Sulpiride.

26.Deshpande AA et al[25] (1997)developed novel controlled release gastric retention system, which consists of a matrix tablet, coated with a permeable membrane. Tablets containing soluble drug Chlorpheniramine maleate and poorly soluble drug Riboflavin were compressed. Studies showed that, the chances of

elimination through the pylorus greatly reduced due to tablets expansion and the tablet expelled out of stomach at the end of the drug release.

AIM AND OBJECTIVES

- To Formulate GRTS for Ziprasidone Hydrochloride using the Microballons approach.

- Microballons are drug entrapped hollow Microspheres which will float on the gastric content by virtue of having low density.

- The aim is to prepare microballons using two different polymeric systems viz:

  1. Ethyl Cellulose
  2. Hydroxy Propyl Methyl Cellulose

- The Microballons shall be characterized and in vitro dissolution profile shall be evaluated.

- The aim of the present work is to formulate Floating Microcapsules for prolonged delivery of Ziprasidone Hydrochloride using Ethyl cellulose as release retarding polymer, and Hydroxy Propyl Methyl Cellulose as pore former.

- The formulation optimization was done using full factorial 2^3 design of experiments matrix.

- In-vitro dissolution study on the formulations was performed in 0.1N HCL medium.

PLAN OF WORK

- **Step: 1 Preformulation Study**
    - API Characterization
        - Physical Appearance
        - Solubility studies
    - Drug-Excipient Compatibilty Studies
        - Physical Compatibility
        - FT-IR Spectrophotometry
    - Analytical Method Development

- **Step: 2 Selection of the method(Solvent Evaporation Technique)**
- **Step: 3 Design of experiments by 2^3 full factorial design**
- **Step: 4 Optimization through results of evaluation**
- **Step:5 In-vitro dissolution testing**
- **Step:6 Data interpretation and reporting the results**

DRUG PROFILE[26]

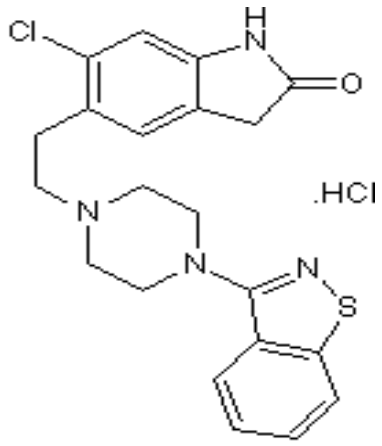
ZIPRASIDONE HYDROCHLORIDE

Chemical name : 5-[2-[4-(1,2-Benzisothiazol-3-yl)-1 -piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H* indol- 2-one hydrochloride

Empirical formula : $C_{21}H_{21}ClN_4OS.HCL$

Molecular weight : 449.4

Structure :



Physicochemical Profile

Description:

white to off-white crystalline powder

Solubility:

Soluble to 10 mm in DMSO

PHARMACEUTICAL PROFILE

Dosage Forms and dose:

Capsules: 20 mg, 40 mg, 60 mg, 80 mg

I.M Injection: 20 mg/ml

Pharmacopoeial status:

United States Pharmacopoeia

Storage:

It should be stored in an airtight container and protected from light

ANALYTICAL PROFILE

Spectrophotometry:

Spectrophotometric determination of Ziprasidone Hydrochloridein 0.1 HCL with the the λmax at 318nm has been reported.

PHARMACOKINETIC PROFILE

Oral absorption:

60%

Plasma half life:

7 hours.

Protein Binding:

99 % (Plasma proteins)

PHARMACOLOGICAL PROFILE

Therapeutical category:

Antipsychotic

Mechanism of action:

Ziprasidone's antipsychotic activity is likely due to a combination of its antagonistic function at D2 receptors in the mesolimbic pathways and at 5HT2A receptors in the frontal cortex. Alleviation of positive symptoms is due to antagonism at D2 receptors while relief of negative symptoms are due to 5HT2A antagonism.

THERAPEUTIC/CLINICAL USES:

Ziprasidone Hydrochloride is indicated for the treatment of schizophrenia and related psychotic disorders.

ADVERSE EFFECTS

CNS:

Dizziness, Drowsiness, Dystonia, Hypertonia, Asthenia, Akathisia, Extrapyramidal reactions, Agitation, Headache, Insomnia, Personality disorder, Paresthesia, Speech disorder, Neuroleptic malignant syndrome, Seizures and Suicide attempt.

CV:

Orthostatic hypotension, Hypertension, Tachycardia, Arrhythmias (from prolonged QT interval)

EENT:

Abnormal vision and Rhinitis

GI:

Nausea, Vomiting, Diarrhea, Constipation, Dyspepsia, Dry mouth and Anorexia

MUSCULOSKELETAL:

Myalgia

RESPIRATORY:

Cough and Cold symptoms

SKIN:

Urticaria,Rrash, Fungal dermatitis, Diaphoresis and Photosensitivity

OTHER:

Accidental injury, Pain at I.M. injection site

POLYMER PROFILE

1.HYDROXY PROPYL METHYL CELLULOSE[27]

Synonyms:

Hydroxy Propyl Methyl Cellulose; HPMC; Methocel; Benecel MHPC; Methyl hydroxy propyl cellulose; Methylcellulose propylene glycol ether; Metolose.

Chemical name:

Cellulose hydroxy propyl methyl ether

Functional category:

Coating agent, Film-former, Rate-controlling polymer for sustained release, stabilizing agent, Suspending agent, Tablet binder, Viscosity-increasing agent.

Physicochemical Properties

Description:

White to slightly off white powder, free flowing powder

Methoxyl content:

19-24%

Hydroxypropyl content:

7-12%

Bulk density:

0.12 – 0.15 g/ml

pH (1% content):

5.5-8

Solubility:

HPMC K4M is a medium viscosity polymer which is soluble in water

Viscosity:

4000(mpas)

Applications:

- Hypromellose is widely used in oral, ophthalmic and Topical pharmaceutical formulations.In oral products; Hypromellose is primarily used as a tablet binder, in film coating, and as a matrix for use in extended-release tablet formulations.

- Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation process. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in Tablets and Capsules.

- Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film coating solutions, while higher-viscosity grades are used with organic solvents.

- Hypromellose is also used as suspending agent in topical formulations. Hypromellose at concentrations between 0.45-1.0% w/w may be added as thickening agent to vehicles for Eye drops and Artificial tear solutions.
- Hypromellose is also used as an Emulsifier, Suspending agent, and Stabilizing agent in topical gels and Ointments..
- Hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and Food products.

2.ETHYL CELLULOSE

Ethyl cellulose is a chain of β-anhydro glucose units joined together by acetal linkage.

It is prepared from wood pulp or chemical cotton by treatment with alkali and ethylation of the alkali cellulose with Ethyl chloride. Commercial Ethyl Cellulose has an ethoxy content of 43-50 %. A 47 % product softens at 140^{o}C and is soluble in Ethyl Acetate, Benzene, Toluene, Xylem and Butanol. The properties and pharmaceutical applications of Ethyl cellulose are as follows:

Synonyms:

Ethocel

Description:

A tasteless, odourless, free flowing, white to light tan powder.

Specific gravity:

1.14

Softening temperature:

152-162 ^{0} C

Emperical formula and Molecular weight:

Ethyl cellulose with complete Ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6$ $(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$ where *n* can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by Acetal linkages.

Functional Category:

Coating agent, Tablet binder, Tablet filler and Viscosity-increasing agent.

Solubility:

Insoluble in water, glycerin, propylene glycol, but soluble in varying degrees in organic solvents.

Viscosity:

A property of ethyl cellulose such as tensile strength, elongation and flexibility depends largely upon the degree of polymerization, which can be measured by viscosity. Therefore, within each type-based Ethoxyl content there exists low to high viscosity types, based on degree of polymerization

Stability:

It is resistant to alkali both dilute and concentrated but more sensitive to acidic materials than cellulosic ethers.

Applications

1. **Binder in tablets:**

   Ethyl cellulose may be dry blended and wet granulated with a solvent such as alcohol. Tablets made with Ethyl cellulose as binder tend to exhibit poor dissolution and poor drug absorption.

2. **Coating material for tablets:**

   Ethyl cellulose by itself forms a water insoluble film coating. It is commonly used with Hydroxy Propyl Methyl Cellulose to alter the solubility of the film. Other materials may be used for this as well.

3. **Coating material for stabilization**:

   Ethyl cellulose dissolved in Isopropanol is used to coat particles of drugs to form Microcapsules. This type of Microcapsules slows dissolution of the drug as a function of Microcapsule wall thickness.

3.TWEEN-80

1. Nonproprietary Names:

BP: Polysorbate 80

JP: Polysorbate 80

PhEur: Polysorbate 80

USP-NF: Polysorbate 80

2. Synonyms:

Polysorbate 80 Atlas E; Armotan PMO 20; Capmul POE-O; Cremophor PS 80; Crillet 4; Crillet 50; Drewmulse POE-SMO; Drewpone 80K; Durfax 80;Durfax 80K; E433; Emrite 6120; Eumulgin SMO; Glycosperse O-20; Hodag PSMO-20; Liposorb O-20; Liposorb O-20K; Montanox80; polyoxyethylene 20 oleate; polysorbatum 80; Protasorb O-20; Ritabate 80; (Z)-sorbitan mono-9-octadecenoate poly(oxy1,2-ethanediyl) derivatives; Tego SMO 80; Tego SMO 80V; Tween 80**.**

3. Chemical Names and CAS Registry Numbers:

Polysorbate 80 Polyoxyethylene 20 sorbitanmonooleate (9005-65-6)

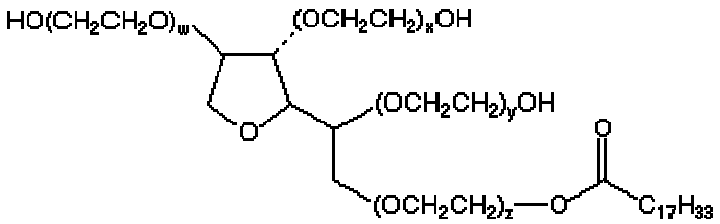
4 .Empirical Formula and Molecular Weight:

$C_{64}H_{124}O_{26}$, Mol. wt: 1310

5. Functional Category

Dispersing agent; Emulsifying agent; Nonionic surfactant; Solubilizingagent; Suspending agent and Wetting agent.

6. structure:



Polysorbate 80
(Sum of w, x, y, and z is 20)

7. Description:

Polysorbates have a characteristic odor and a warm, somewhat bitter taste. Their colors and physical forms at 258^{0c} , although it should be noted that the absolute color intensity of the products may vary from batch to batch and from manufacturer to manufacturer.

8. Incompatibilities:

Discoloration and/or precipitation occur with various substances,especially phenols, tannins, tars, and tarlike materials. The antimicrobial activity of Paraben preservatives is reduced in the presence of Polysorbates.

9. Stability and Storage Conditions:

Polysorbates are stable to electrolytes and weak acids and bases;gradual saponification occurs with strong acids and bases. The oleicacid esters are sensitive to oxidation. Polysorbates are hygroscopic and should be examined for water content prior

to use and dried if necessary. Also, in common with other polyoxyethylene surfactants,prolonged storage can lead to the formation of peroxides. Polysorbates should be stored in a well-closed container, protected from light, in a cool and dry place.

10.Applications in Pharmaceutical Formulation:

Polysorbates containing 20 units of Oxyethylene are hydrophilic nonionic surfactants that are used widely as Emulsifying agents inthe preparation of stable oil-in-water pharmaceutical emulsions. They may also be used as Solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions.They have been found to be useful in improving the oral bioavailability of drug molecules that are substrates for P-glycoprotein.

4.ISOPROPYL ALCOHOL

Chemical Name:

Isopropyl alcohol

Formula:

C_3H_8O

Synonym:

Propan-2-ol, 2-propanol or the abbreviation

Physical and chemical properties

Molecular weight:

60.01 g/mole

Color:

Colorless

Nature :

Liquid

Odour :

Pleasant

Taste :

Slight bitter

Density:

0.786 g/cm^3

Boiling Point:

82.5^o C

Solubility:

Easily soluble in Cold water, Hot water, Methanol, Diethyl ether, n-octanol, Acetone.Insoluble in salt solution.Soluble in benzene.Miscible with most organic solvents including Alcohol, Ethyl alcohol and Chloroform.

Melting point:

89°C (with decomposition)

Functional category:

Granulating agent

Applications:

- It is used dissolves a wide range of Non –polar compounds. It also evaporates quickly and is relatively Non-toxic, compared to alternative solvents.
- It is used widely as a solvent and as a cleaning fluid, especially for dissolving Lipophilic contaminants such as oils.
- As a biological specimen preservative, Isopropyl alcohol provides a comparatively non-toxic alternative to Formaldehyde and other synthetic preservatives. Isopropyl alcohol solutions of 90-99% are optimal for preserving specimens, although concentrations as low as 70% can be used in emergencies.
- Disinfecting pads typically contain a 60–70% solution of Isopropyl alcohol in water. Isopropyl alcohol is also commonly used as cleaner and solvent in industry.
- Isopropyl alcohol is often used in DNA extraction. It is added to a DNA solution in order to precipitate the DNA into a 'pellet' after centrifuging the DNA. This is possible because DNA is insoluble in Isopropyl alcohol

Stability and Storage:

Store in a segregated and approved area. Keep container in a cool, well-ventilated area. Keep container tightly closed and sealed until ready for use. Avoid all possible sources of ignition spark or flame.

MATERIALS AND METHODS

The chemicals and reagents used in the study are given in Table 3 and the equipments used are listed in Table 4

Table 3: List of Materials and their Suppliers

S. No.	Name of Materials	Supplier
1	Ziprasidone Hydrochloride	Marko Labs,Mumbai
2	Ethyl Cellulose	Marko Labs,Mumbai
3	Hydroxy Propyl Methyl Cellulose	Marko Labs,Mumbai
4	Dichloromethane	Marko Labs,Mumbai
5	Isopropyl alcohol	S.D fine Chemicals,Mumbai
6	Tween-80	S.D fine Chemicals,Mumbai

Table 4: List of Equipments

S.NO	Equipments	Company
1	Glassware	Borosil,Chennai
2	Stirrer	Remi stirrer2500rpm-Delhi
3	Hot plate	Optics technology-Delhi
4	Tray dryer	Optics technology-Delhi
5	Sonicator	PCI-SS-Delhi
6	Optical microscope	Dalal &co-Chennai
7	UV Spectrophotometer	E2371 spectrophotometer-Mumbai
8	Dissolution apparatus	Campbell electronics-Mumbai
9	Scanning electron microscope	Hitachi model SU 1500,JEOL JSM T330A scanning microscope-Japan
10	FTIR 200 spectrometer	Spectrum one Perkin Elmar-USA

METHODS

Preformulation Studies[28]:

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of Physico-chemical properties of a new drug substance alone and when combined with the excipients, to generate data useful to the formulator in developing safe, potent, bio-available and efficacious dosage form, which can be mass produced. The goals of preformulation studies are,

- To establish the physicochemical parameter of new drug substances.
- To establish the kinetic rate profile.
- To establish physical characteristics.
- To establish compatibility with the common excipients.

Hence, the following parameters were selected for the preformulation studies of the pure drug.

Identification of pure drug:

Identification of Ziprasidone Hydrochloride was examined by FT-IR and was compared with the spectrum of Ziprasidone Hydrochloride.

Solubility Analysis:

Solubility analysis was done to select suitable solvents/solvents to dissolve the drug, Polymer as well as various excipients used for the formulation of microspheres.

Melting point determination:

Melting point of Ziprasidone was determined by using Melting point apparatus (Capillary tube).melting point of a drug sample is a first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by lowering as well as widening in the melting point range.

Compatibility studies:

Compatibility of the Ziprasidone Hydrochloride with Ethyl cellulose and Hydroxy Propyl Methyl Cellulose used to formulate Microballons was established by FT-

IR. Spectral analysis of Ziprasidone, Ethyl Cellulose and Hydroxy Propyl Methyl Cellulose and combination of the Ziprasidone with Polymer was carried out to investigate any changes in chemical composition of the drug after combining it with the excipients.

Determination of $\lambda_{max:}$.

100 mg of Ziprasidone was dissolved in Methanol and diluted to 100ml with the 0.1N HCL 1ml of this solution was diluted to 10 ml with 0.1N HCL this gives the solution of concentration 100 mcg/ml. from this 1ml solution was transferred in to 10ml volumetric flask and diluted with 0.1N HCL this gives the solution of concentration 10 mcg/ml and this solution was examined between 278 nm. The maximum obtained in the graph was considered as λmax. The solution has shown an absorption maximum at 278nm.

STANDARD CALIBRATION CURVE FOR ZIPRASIDONE HYDROCHLORIDE

In simulated gastric fluid (Acidic buffer) pH 1.2

Weighed quantity of Ziprasidone Hydrochloride (100mg) was dissolved in pH1.2 buffer and the volume was made up to 100ml with the same medium. From this stock solution, serial dilutions were made to obtain the solutions in concentration ranging from 5-60µg/ml. The absorbance was measured at 300nm.

FORMULATION OF MICROBALLONS[29,30,31,32,33]:

Trial and error method: (Preliminary experiments)

Previously many trials were run for the preparation of Floating Microcapsules of Ziprasidone Hydrochloride by Solvent Evaporation Technique. Trials were made by changing the temperature and stirring speed, concentration of the Ethyl Cellulose,Hydroxy propyl methyl cellulose and Ziprasidone concentration. After so many trials, it was concluded that temperature plays a very critical role in the formation of Floating Microcapsules, it is a continuous process of stirring, with the combination of Hydrophilic Non –ionic surfactant and Ethyl cellulose as Release retarding polymer, and Hydroxy Propyl Methyl Cellulose as pore former. Every step in the process was optimized by performing experiments through trial and error method.

Preparation of Floating Microspheres:

Ziprasidone Hydrochloride Floating Microspheres were prepared by the Solvent Evaporation Technique. The following steps were followed for the preparation of the Floating Microcapsules

- Ziprasidone, Ethyl cellulose and Hydroxy Propyl Methyl Cellulose were dissolved in solvent mixture of 15 ml of Isopropyl alcohol and 15 ml of Dichloromethane.
- The solution was filled into a syringe fitted with 22 Gauge needle.
- It was dropped at a rate of 50 drops/minute into a beaker containing 500 ml water with 2.5 ml Tween-80 as the continuous phase.
- The continuous phase was stirred using 3 blade Remi stirrer at 500 rpm.
- After complete addition of the Drug-polymer solution, the mixture was allowed to stir for 2 hours.
- The Microcapsules Floating on the top of the continuous phase were collected and dried at 40^0C for 1 hour in a hot air oven. The Floating Microcapsules were Stored in an air tight containers till taken for further evaluation.
- The dried Microcapsules were weighed and the yield was determined.

DOE[34]:

- A full 2^3 factorial design14-15 was introduced to optimize the formulation of Ziprasidone loaded EC+ HPMC Microballons using the Solvent Evaporation Technique
- Entrapment Efficiency was considered as a measurable parameter for this study.
- A design matrix comprising of 8 experimental runs was constructed using DOE Pro XL Software to investigate the effect of three factors.

Ziprasidone concentration as (A),
EC concentration as (B) and
HPMC concentration as (C).

- on the response variable i.e. % Drug released at 1 hour (D_1) and percentage of Drug release at 8 hours (D_8) were considered as measurable parameters.
- Volume of solvent (50 ml), ratio of IPA and DCM (1:1), volume of aqueous phase (500 ml) concentration of Tween (2.5ml), stirring speed (500 rpm) and temperature (ambient) were kept constant.

Table 5:Full factorial DOE Floating Microcapsules of Ziprasidone Hydrochloride

Formulation	Ziprasidone	Ethyl cellulose	Hydroxy propyl methyl cellulose
F1	**L**	**L**	**L**
F2	**L**	**L**	**H**
F3	**L**	**H**	**L**
F4	**L**	**H**	**H**
F5	**H**	**L**	**L**
F6	**H**	**L**	**H**
F7	**H**	**H**	**L**
F8	**H**	**H**	**H**

L-low, **H-**high ;

Table 6:DOE (mg/unit)

S.NO	Ingredients	LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
		F1	F2	F3	F4	F5	F6	F7	F8
1	ZIPRASIDONE	100	100	100	100	500	500	500	500
2	EC 7cps	200	200	500	500	200	200	500	500
3	HPMC 6cps	200	500	200	500	200	500	200	500

ZIPRASIDONE- L-100mg, H-500mg,

EC- L-200mg, H- 500mg,

HPMC- L- 200mg, H- 500mg.

PHOTOGRAPHS OF THE FORMULATIONS OF HIGH ENTRAPMENT EFFICIENCY

FIG 15:F3LHL

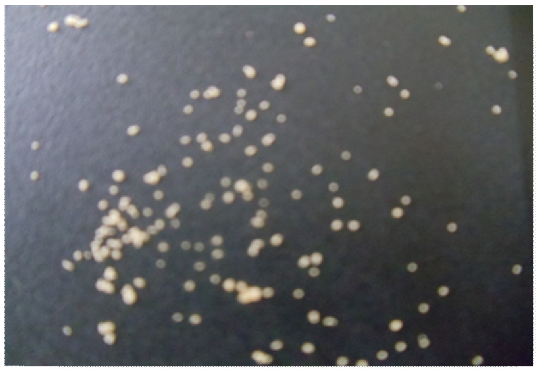


FIG15.3: F8: HHH

FIG 15.2:F5: HLL

FIG 15.1:F4: LHH

FIG 15.4:F7: HHL

FIG 15.5: F optima

CHARACTERIZATION OF THE ZIPRASIDONE HYDROCHLORIDE FLOATING MICROCAPSULES

Particle size[35]:

Determination of average particle size of Ziprasidone Hydrochloride Floating Microcapsules was carried out by Optical Microscopy in which stage micrometer was

employed. A minute quantity of Microcapsules was suspended in Liquid paraffin and spread on a clean glass slide and average size of 100 Microcapsules was determined in each batch.

Surface Morphology[34]:

Scanning Electron Microscopy has been used to determine Particle distribution, Surface topography, Texture and to examine the Morphology of fractured or Sectioned surface.SEM studies were carried out by using JEOL JSMT-330A Scanning Microscope (Japan).The samples of SEM were prepared by lightly sprinkling the Microcapsules powder on a double adhesive tape, which was stuck on an Aluminum stub. The stubs were then coated with gold to thickness of about 300A using a Sputter coater. The photomicrographs were taken with the help of SEM analyzer.

Drug Entrapment Efficiency[35]:

The Microcapsules sample was powdered using Mortar and Pestle. An accurately weighed sample of 20mg of Microspheres was dispersed in 47.5 ml of 0.1N HCL and 2.5ml of Methanol, and sonicated for 30 minutes at a temperature of 37.5^0C.The resultant solution was filtered, and the filtrate was suitably diluted with 0.1N HCL .Absorbance was measured at 278nm by using UV Spectroscopy.

$$\%\text{Entrapment efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

The entrapment efficiency values were determined in triplicate.

Estimation of Drug Content:

Drug content in the Microcapsules was calculated by UV Spectrophotometric method. A sample of Microcapsules equivalent to 100 mg was dissolved in 25 ml Methanol and the volume was adjusted upto 100 ml using 0.1N HCL. The solution was filtered through Whatman Filter Paper. Then the filtrate was assayed for drug content by measuring the absorbance at 278 nm after suitable dilution.

Percentage Yield:

The percentage yield of the prepared microspheres was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

In-vitro dissolution[36,37,38,39]:

Dissolution is the main evaluation study conducted for the estimation of the drug release from the dosage form. USP-TYPE II apparatus was selected for the study. Formulations with Entrapment Efficiency more than 65% were selected for the study. The Microcapsules equivalent to 100mg of drug were weighed accurately and filled in the capsule shells. Dissolution profiles were carried out in the following media:

(1) 0.1N HCL for 2 hours

The parameters for dissolution apparatus for all the above runs were kept constant as described below:

Type of apparatus:

USP II.

RPM:

50

Temperature:

N=8 samples

$37.5^0 \pm 0.5^0 C$

Preparation of Buffer Solutions:

1. **Preparation of pH 1.2 Buffer:** place 8.5 ml of Hydrochloric acid in 1000 ml of Distilled water.

METHOD FOR DISSOLUTION:

A total of 8 formulations were selected for the dissolution with Drug Entrapment more than 65%. These formulations were taken as n=8 for the dissolution. The method dissolution is as follows.

In vitro dissolution testing was conducted on Microcapsules equivalent to 100 mg of Ziprasidone.

- Microcapsules were filled in hard gelatin capsules shells
- USP Type I apparatus was used
- Media 900 ml 0.1N HCL
- RPM: 50 rpm
- Time points: 0. 0.5, 1, 2, 4 and 8 hours
- Estimation by UV spectrophotometry.

- The dissolution vessels must be filled with the respective dissolution media. The dissolution parameters such as temperature, stirring speed must be set before starting of the dissolution.
- As the dissolution assembly reaches the temperature, sometime must be allowed for the paddles to rotate, after which the sample should be dropped carefully and the time must be noted.
- At the prescribed time intervals, aliquots(5ml) must be withdrawn with sampling tubes, at the same time equal quantity(5ml) of dissolution medium must replaced to maintain the volume of the medium.
- Withdrawn aliquots must be suitably diluted with the dissolution medium, and analyzed spectrophotometrically.
- Drug release was calculated and tabulated.

MECHANISM OF DRUG RELEASE[40]

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as

i. Cumulative percentage drug released Vs Time (*In-vitro* drug release plots)

ii. Cumulative percentage drug released Vs Square root of time (Higuchi's plots)

iii. Log cumulative percentage drug remaining Vs Time (First order plots)

iv. Log percentage drug released Vs Log time (Peppas plots)

Higuchi release model:

To study the Higuchi release kinetics, the release rate data was fitted to the following equation.

$$F = K_H.t^{½}$$

Where, 'F' is the amount of drug release,

'K_H' is the release rate constant, and

't' is the release time

When the data is plotted as a cumulative percentage drug release versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer and Peppas release model:

The release rate data were fitted to the following equation,

$$Mt / M\infty = K_M. t^n$$

Where, $Mt / M\infty$ is the fraction of drug release,

'K_M' is the release constant, 't' is the release time,'n' is the diffusional exponent for the drug release that dependent on the shape of the matrix dosage form. When the data is plotted as log percentage release versus log time, yields as straight line with a slope equal to 'n' and the 'K' can be obtained from Y – intercept. For Non-Fickian release the 'n' values falls between 0.5 and 1.0 while for Fickian (case I) diffusion n= 0.5 and Zero order release (case-II transport)

n= 1.0.

Zero order release rate kinetics:

To study the zero-order release kinetics the release rate date are fitted to the following equation.

$$F = K_0t$$

Where 'F' is the fraction of drug release,

'K_0' is the release rate constant and

't' is the release time.

When the data is plotted as cumulative percentage drug release versus time, if the plot is linear then the date obeys Zero-order release kinetics, with a slope equal to K_0.

First order model:

This model has also been used to describe absorption and/or elimination of some drugs, The release of the drug which followed first order kinetics can be expressed by the equation:

$$\log C = \log C_0 - Kt / 2.303$$

Where, C_0 is the initial concentration of drug,

k is the first order rate constant, and

t is the time .

The data obtained are plotted as log cumulative percentage of drug remaining *vs*. time which would yield a straight line with a slope of -K/2.303.

RESULTS AND DISCUSSIONS

A total of eight formulations of Ziprasidone Hydrochloride Floating Microcapsules were formulated by Solvent Evaporation Technique using Design Of Experiment approach. The formulations were subjected to evaluation parameters like Particle size, Surface morphology, Drug entrapment efficiency and In-vitro drug release studies.

PREFORMULATION STUDIES

Identification of Pure Drug

FT-IR Spectroscopy:

The FT-IR spectrum of the pure drug was found to be similar to the standard Microcapsules were shown in the Figures 16 and 17 respectively.

Melting Point Determination:

The melting point of the obtained drug sample was found to be 256^0C which is the reported range of 255^0C -257^0C.It complies with the USP standards thus indicating the purity of the drug soluble.

Solubility Analysis:

Ziprasidone Hydrochloride sample was found to be insoluble in water,2-propanol and Ethanol, sparingly soluble in Acetone. Soluble in 0.1N Sodium hydroxide .Solubility analysis is important because the drug has to dissolve in the solvents also in the dissolution medium used.

Compatibility studies:

From the FT-IR spectra of the pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristics peaks of Ziprasidone Hydrochloride were present in the combination spectra thus indicating the compatibility of the drug with the polymer used.

FIG 16: FT-IR OF ZIPRASIDONE HYDROCHLORIDE

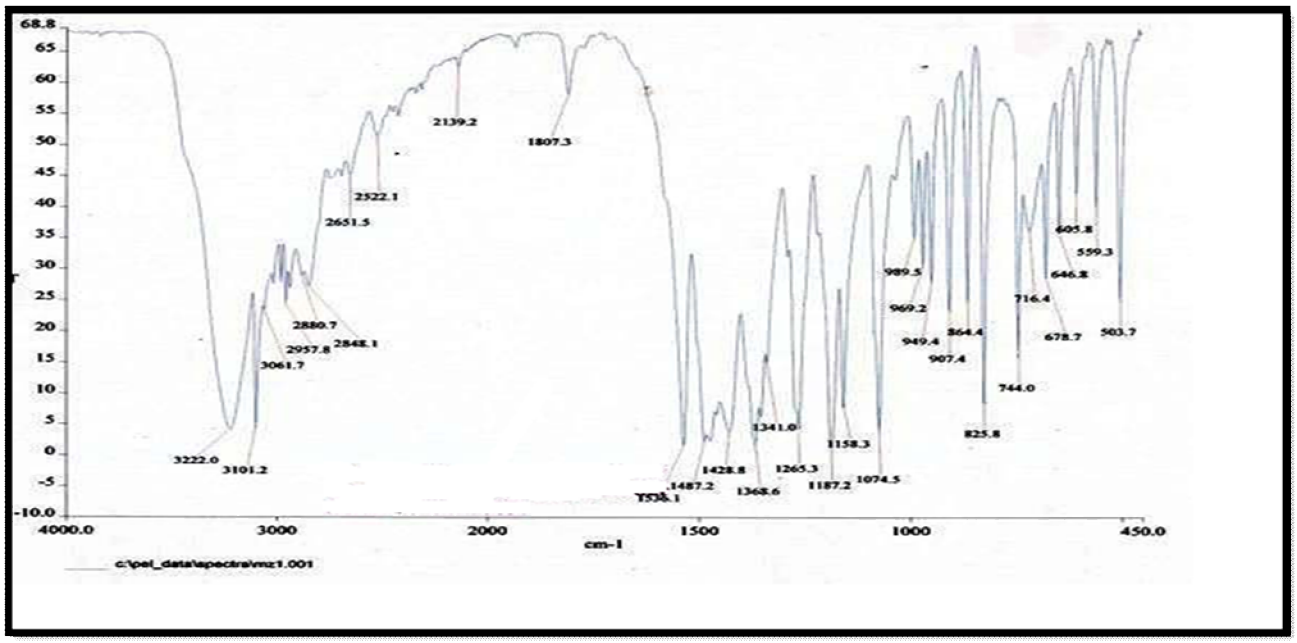
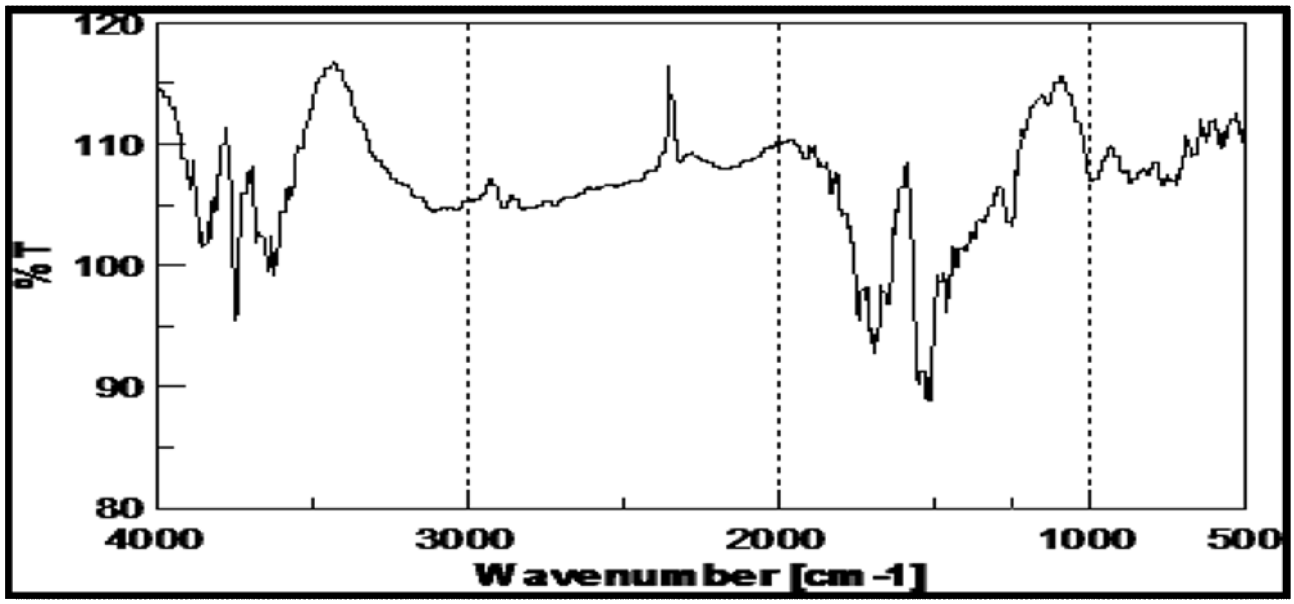


FIG 17: FT-IR OF OPTIMIZED FORMULATION



The FTIR spectrum for the drug loaded Microspheres indicates that there is no chemical interaction between the drug and the polymers used during the process of Microencapsulation.

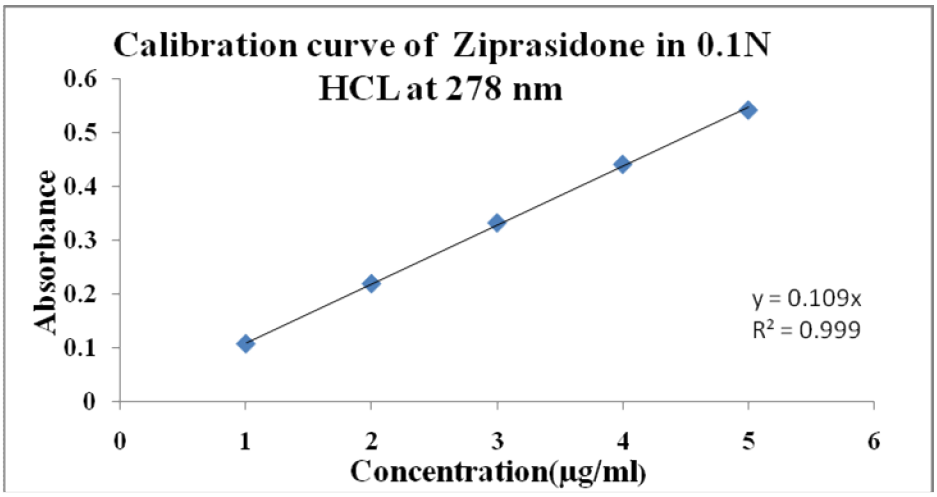
STANDARD CALIBRATION CURVE OF ZIPRASIDONE HYDROCHLORIDE IN BUFFERS (PH 1.2):

Standard calibrated values of Ziprasidone Hydrochloride in 0.1N HCL were tabulated as follows. They were at different concentrations ranging from 1-5µg/ml in acidic buffer (pH 1.2). The curves of respective values are also presented below.

Table 7: CALIBRATION VALUES OF ZIPRASIDONE HYDROCHLORIDE IN 0.1N HCL

S.NO	CONCENTRATION	ABSORBANCE
1	1	0.107
2	2	0.219
3	3	0.332
4	4	0.441
5	5	0.542

Figure 18:Calibration curve of Ziprasidone Hydrochloride



Percentage yield:

Percentage yield of different formulations,F1-F8,were calculated and the yield was found to be above 45%.The results are tabulated in the Table 8.The results indicate that the Solvent Evaporation Technique gives excellent yield of the Floating Microcapsules.

Table 8: PERCENTAGE YIELD OF FORMULATION

Formulation	Percentage Yield(%w/w)
F1	**54.82**
F2	**59.45**
F3	**77.92**
F4	**80.23**
F5	**46.87**
F6	**48.57**
F7	**65.97**
F8	**68.97**

DISCUSSION:

The yield of microcapsules seems to depend on the concentration of polymer in the preparation. For formulation F3 , F4, F7 and F8, where the Ethyl cellulose concentration is 500mg, the yields are > 60%.

For formulations with low Ethyl cellulose concetration, the yileds are in the range of 45 to 55%.

CHARACTERIZATION OF MICROBALLONS

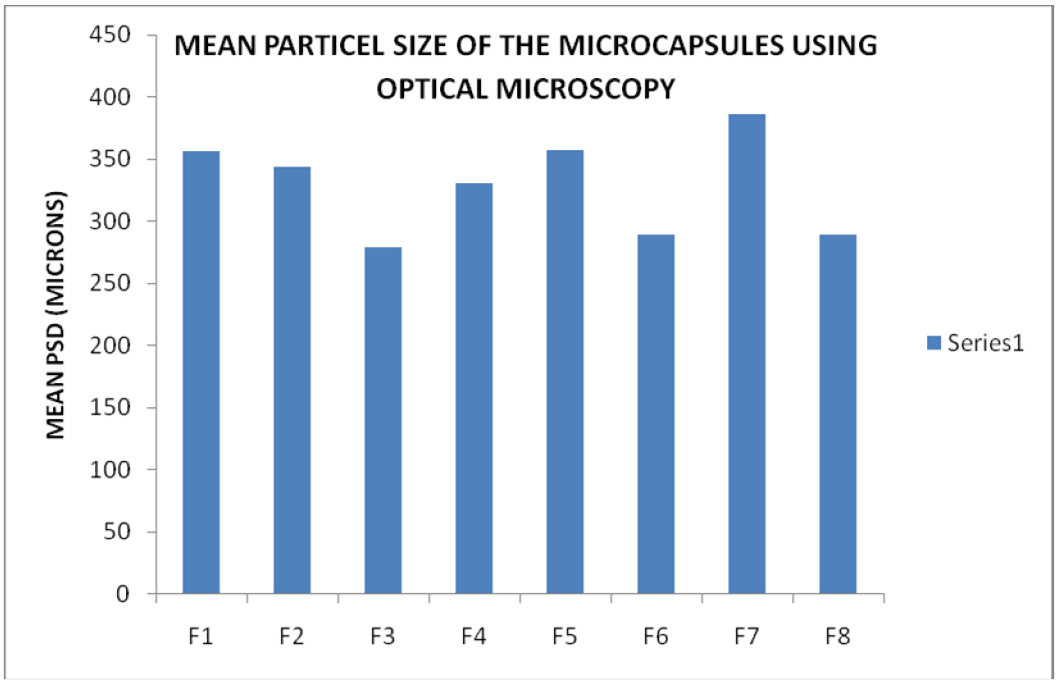
Particle size analysis:

Particle size distribution of Microballons was determined by Optical Microscope fitted with an Ocular Micrometer and Stage Micrometer.The particle sizes of the Microcapsules were found in the range of(65-525µm) for 8formulations(DOE).The particle size of the formulations were shown in the table.

Table9: MEAN PARTICLE SIZE OF THE MICROCAPSULES OF THE FORMULATIONS.

FORMULATION	MEAN PARTICLE SIZE(D90) (µm)
F1	355.86
F2	344.86
F3	278.98
F4	330.77
F5	357.29
F6	288.86
F7	386.55
F8	289.26

Figure 19:Mean Particle Size of the Microcapsules using Optical Microscopy



DISCUSSION:

For all formulations, the Microspheres are in the average particle size range of 278 to 386 µm. The particle size distribution is independent of the formulation and is dependent more on the process followed.

Shape and surface morphology

Surface morphology and internal cross sectional structure of the Floating Microcapsules were investigated with Scanning Electron Microscope.SEM photomicrographs of the blank Microcapsules, Optimized formulation were shown in the figures. The Microcapsules were smooth, spherical and discrete particles. Very less particulate matter of the drug were seen on the surface of the Microcapsules indicating uniform distribution of the drug in the polymer network.

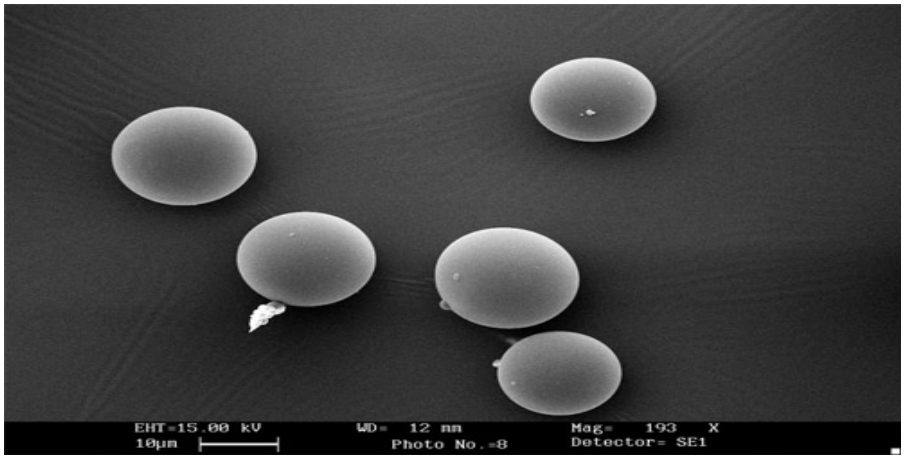


Fig 20: SEM of blank microcapsules

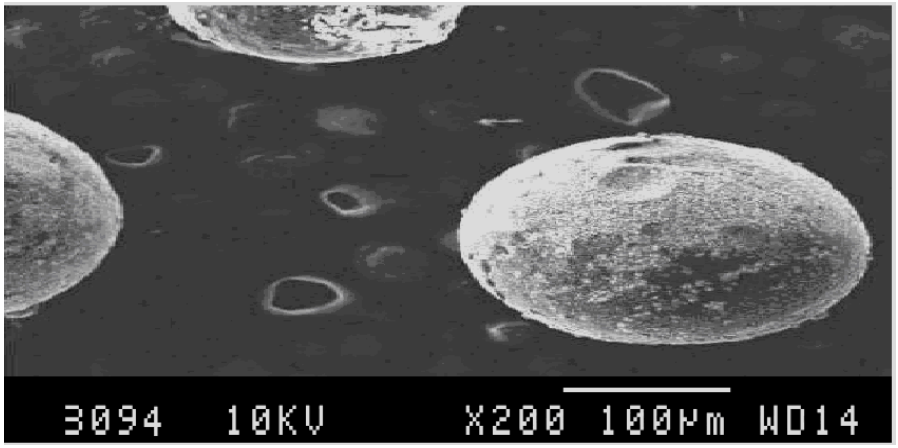


Fig 21:SEM of foptima

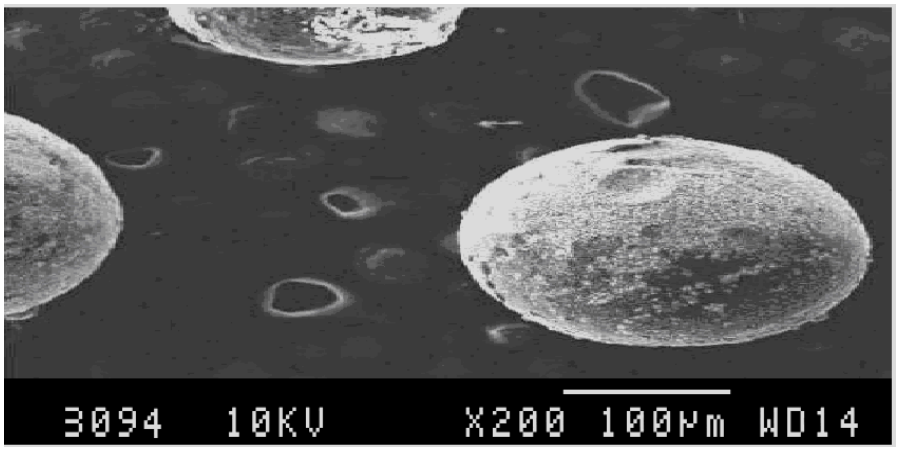


Fig 22: SEM of Foptima2

DISCUSSION:

The SEM images show Spherical Microspheres with a rough and porous surface. The Microspheres for the scale up batch (Fig 22) shows that the Microspheres obtained for the scale up batch are reproducible in surface characteristics.

DRUG LOADING AND ENTRAPMENT EFFICIENCY:

Table10: ENTRAPMENT EFFICIENCIES OF THE FORMULATIONS.

FORMULATION	ENTRAPMENT EFFICIENCY
F1	60.39
F2	68.58
F3	88.00
F4	78.61
F5	69.97
F6	70.41
F7	85.27
F8	88.70

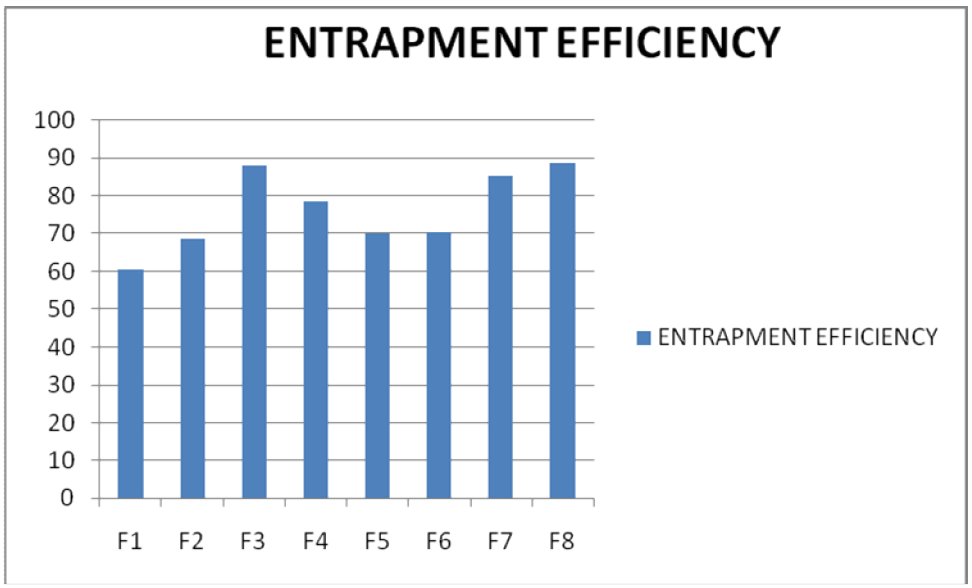


Figure 23:Entrapment Efficiency

DISCUSSION:

The drug Entrappment Efficiency is dependent on the level of Ethyl cellulose in the formula. For formulations with Ethyl cellulose is 500 mg, the Entrappment Efficiency is> 80%. For formulations with Ethyl cellulose levels at 200 mg, the Entrapment Efficiency is around 6o to 75%

IN VITRO BUOYANCY STUDIES

The duration of floatation for all the batches of Microballons was evaluated as follows:

- Quantity of Microballons equivalent to 100 mg of Ziprasidone Hydrochloride was accurately weighed out for each batch.
- This amount was added to a 500 ml glass beaker containing 250 ml of 0.1N HCL(medium). A three blade remi stirrer was fitted into the medium.
- The medium was stirred at 50 rpm for a period of 12 hours
- The behavior of the Microcapsules were observed at 2, 4, 8 and 12 hours interval and the visual observations were noted.

Table 11:IN VITRO BUOYANCY STUDIES

S. No.	Formulation No.	Time (Hours)				
		0	2	4	8	12
1	F1	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface
2	F2	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface
3	F3	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping
4	F4	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping
5	F5	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed	The clumps of ethyl cellulose are formed	The clumps of ethyl cellulose are formed on the

				on the surface	**on the surface**	**surface**
6	**F6**	**Floating without clumping**	**Floating without clumping**	**The clumps of EC are formed on the surface**	**The clumps of EC are formed on the surface**	**The clumps of ethyl cellulose are formed on the surface**
7	**F7**	**Floating without clumping**	**Floating without clumping**	**Floating without clumping**	**Floating without clumping**	**The clumps of ethyl cellulose are formed on the surface**
8	**F8**	**Floating without clumping**	**Floating without clumping**	**Floating without clumping**	**Floating without clumping**	**The clumps of ethyl cellulose are formed on thsurface**

IN-VITRO DISSOLUTION STUDIES:

In vitro release study of Ziprasidone Hydrochloride Floating Microspheres were performed in the following pH media (pH 1.2) at 37^0C ±0.5^0C.

- In vitro dissolution testing was conducted on microcapsules equivalent to 100 mg of Ziprasidone Hydrochloride.
- Microcapsules were filled in hard gelatin capsules shells
- USP Type I apparatus was used
- Media 900 ml 0.1N HCLwith 0.5% Sodium Lauryl Sulphate
- RPM: 50 rpm
- Time points: 0. 0.5, 1, 2, 4 and 8 hours
- Estimation by UV Spectrophotometry.
- The in vitro release profile of Ziprasidone Hydrochloride Floating Microspheres were shown In table 12

Table 12: DISSOLUTION PROFILE AT pH 1.2

TIME		DISSOLUTION PROFILE FOR ZIPRASIDONE HCL FLOATING MICROCAPSULES						
	LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	5.35	7.23	1.09	1.23	30.87	38.32	1.32	5.54
1	9.87	12.45	3.44	5.89	68.61	82.452	5.29	10.88
2	14.79	38.67	10.08	12.44	80.45	88.76	18.35	30.49
4	35.32	70.34	35.85	40.87	88.26	90.12	28.44	60.7
8	80.29	90.35	60.43	68.64	90.23	93.5	78.48	88.58

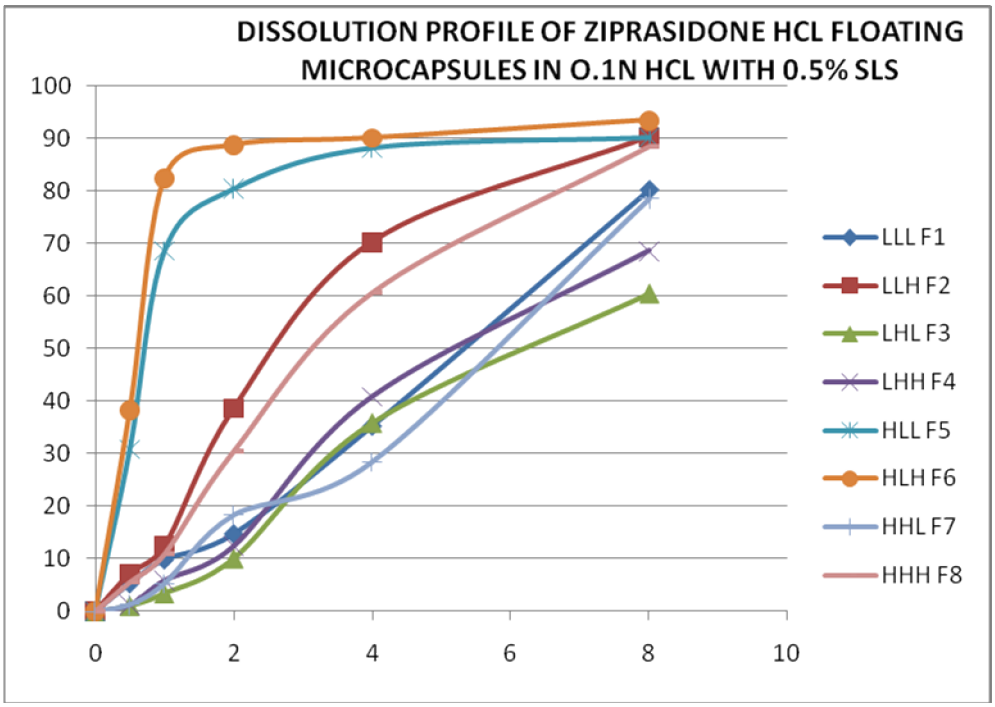


Figure24:Dissloution profile of Ziprasidone Hydrochloride

DISCUSSION:

- The drug release rate and extent is dependent of the ratio of the drug and ethyl cellulose as well as the pore former concentration.
- For formulations with Drug to polymer ratio (F1, F2, F7 and F8), the release is dependent on concentration of HPMC (faster release for higher HPMC levels)
- For formulations with drug to polymer ratio , F3 and F4 the release is very slow (< 70% in 8 hours)
- For formulations with drug to polymer ratio , F5 and F6 the release is very fast (> 80% in 2 hours)

Release kinetics:

Korsemeyer-Peppas Model indicates that the release mechanism is not well known or more than one type of release phenomena could be involved. The 'n' value could be used to characterize different release mechanisms as

:

Table 13: RELEASE EXPONENT (N) VALUES AND DRUG TRANSPORT MECHANISM

Release exponent (n)	Drug Transport Mechanism
0.5	Fickian diffusion (Higuchi Matrix)
0.45< n< 0.89	Non- Fickian diffusion
0.89	Case II transport
Higher than 0.89	Super case II transport

Figure 14:Release Rate of Ziprasidone Hydrochloride from Formulations (F1-F8)

Formulation	R^2				Peppas n
	Zero	First	Higuchi	Peppas	
F1	0.9981	0.9646	0.9272	0.9991	0.943
F2	0.9080	0.9964	0.9524	0.9659	0.874
F3	0.9867	0.9800	0.8689	0.9885	1.353
F4	0.9876	0.9918	0.9165	0.9915	1.146
F5	0.5225	0.9057	0.7911	0.7384	0.322
F6	0.4127	0.7461	0.6958	0.6188	0.244
F7	0.9981	0.9491	0.8834	0.9949	1.091
F8	0.9420	0.9946	0.9491	0.9803	0.927

In order to understand the mechanism of drug release from the Microspheres, the in vitro drug release data were fitted to Korsmeyer and Peppas release model and interpretation of release exponent values enlightens in understanding the release mechanism from the dosage form. The release exponents thus obtained were from 0.874 - 1.353 for the formulations F1- F4 and F7 - F8..

Based on these values we can say that formulations exhibited super case-ii transport. The release exponents formulations F6 and F5 was found to be 0.244 and 0.322Based on these values we can say that formulations exhibited anomalous diffusion mechanism (Non Fickian Transport).

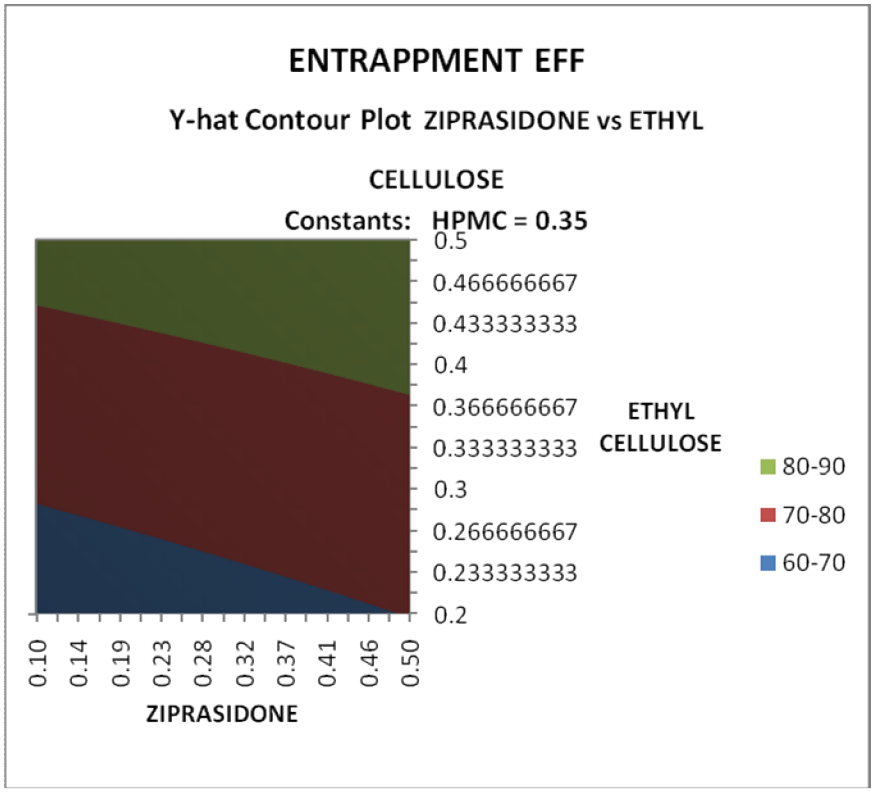
The formulations F1 and F3 showed higher r values for Korsmeyer and Peppas release plot indicating that the drug release from these formulations exhibited Anomalous Diffusion Mechanism. Also the remaining formulations showed higher r values for first order plot indicating that the drug release followed first order kinetics and also the drug release from the microspheres were by both diffusion and erosion

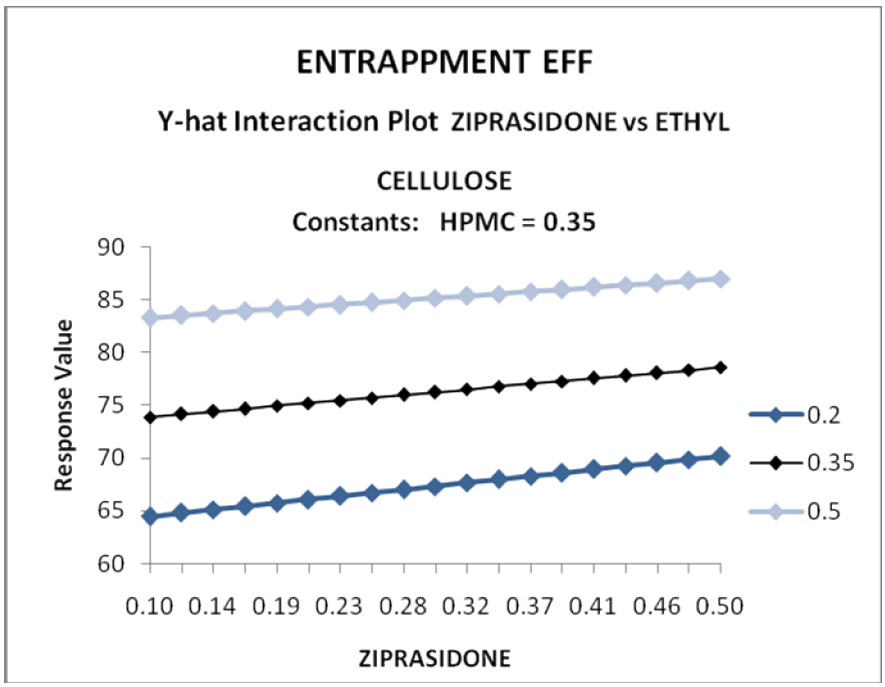
DISCUSSION:

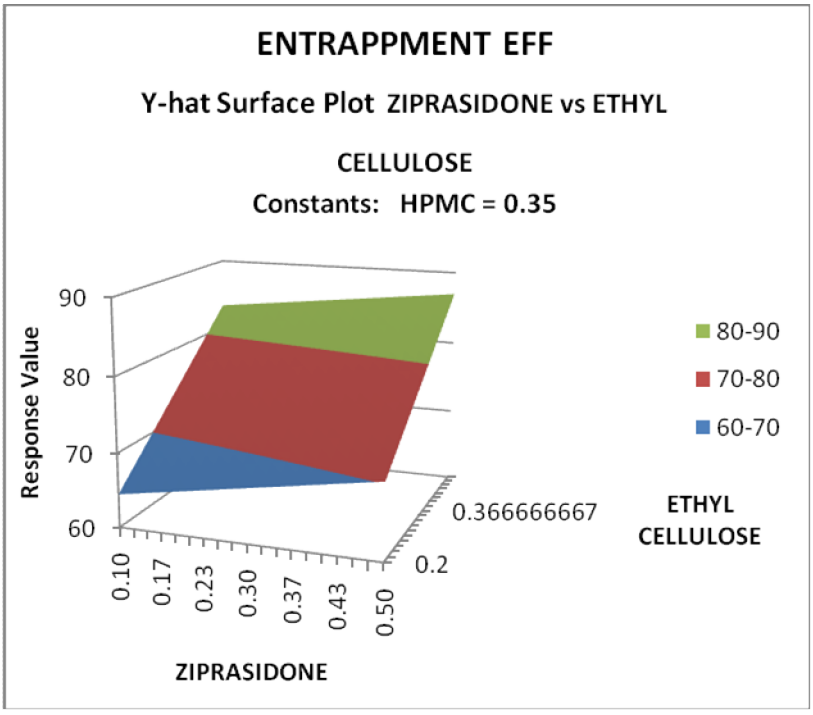
- The release of Ziprasidone Hydrochloride at 1 hour and 8 hours time points were taken as the measurable parameters for running the DOE experiments . The 1 hour time point indicates the rate of release and the 8 hours time point is a measure of the enxtent of the release. The following are for both 1 hour and 8 hours, there is a strong positive interaction between the drug to Ethyl cellulose ratio and the rate and extrent of drug release.
- Hydroxy Propyl Methyl Cellulose 6 cps which is added as the pore former, does not show either positive or negative impact on drug release. However, for formulations having Hydroxy propyl Methyl Cellulose in higher concentrations, the drug release is more complete (at higher Ethyl Cellulose level) than formulations having low level of Hydroxh Propyl Methyl Cellulose

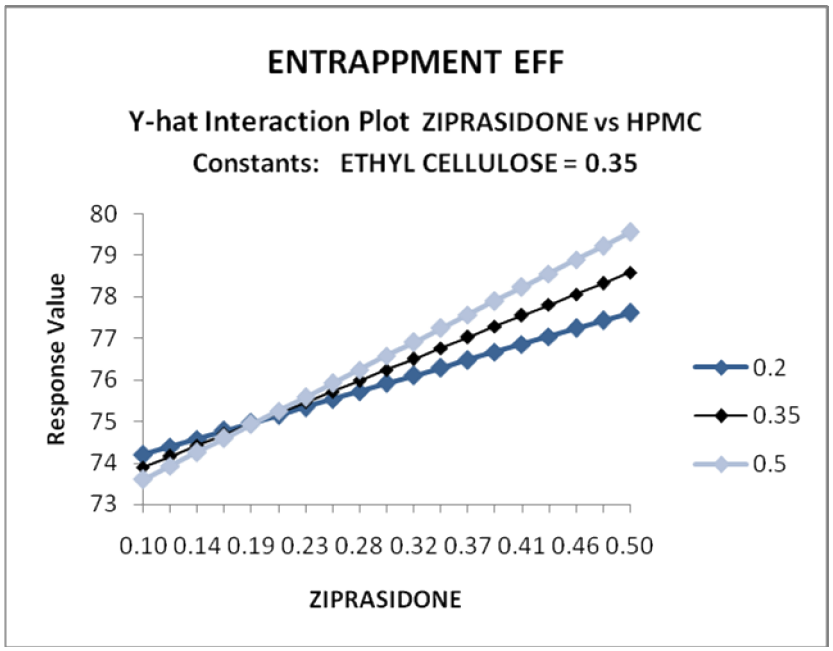
- ❖ The design space for the Ziprasidone Hydrochloride, Ethyl Cellulose and Hydroxy Propyl Methyl Cellulose is defined as per Table 11
- ❖ In order to confirm the design space, 3 formulations within the space were fabricated at a larger scale and evaluted for dissolution profile.
- ❖ These formulations were subjected to accelerated stability studies after filling into hard gelatin capsules shells.

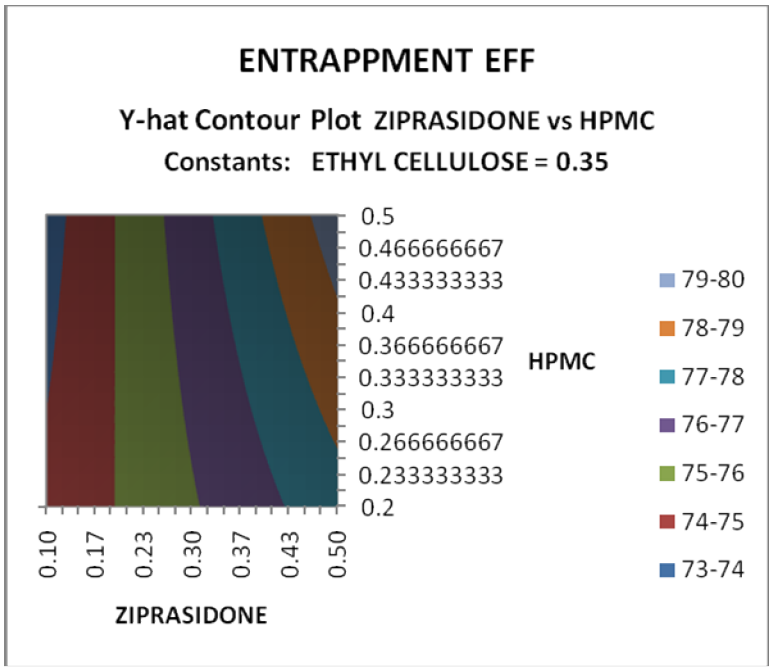
Figure 25:DOE Charts

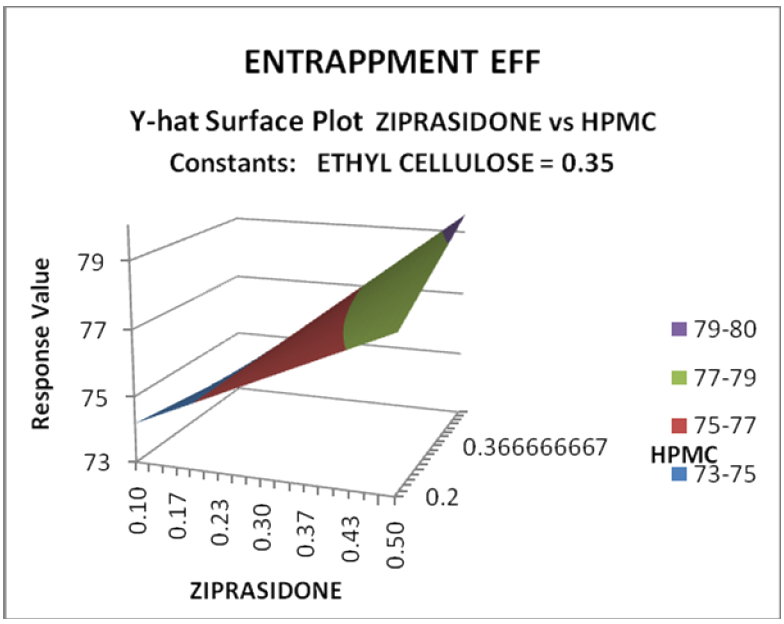


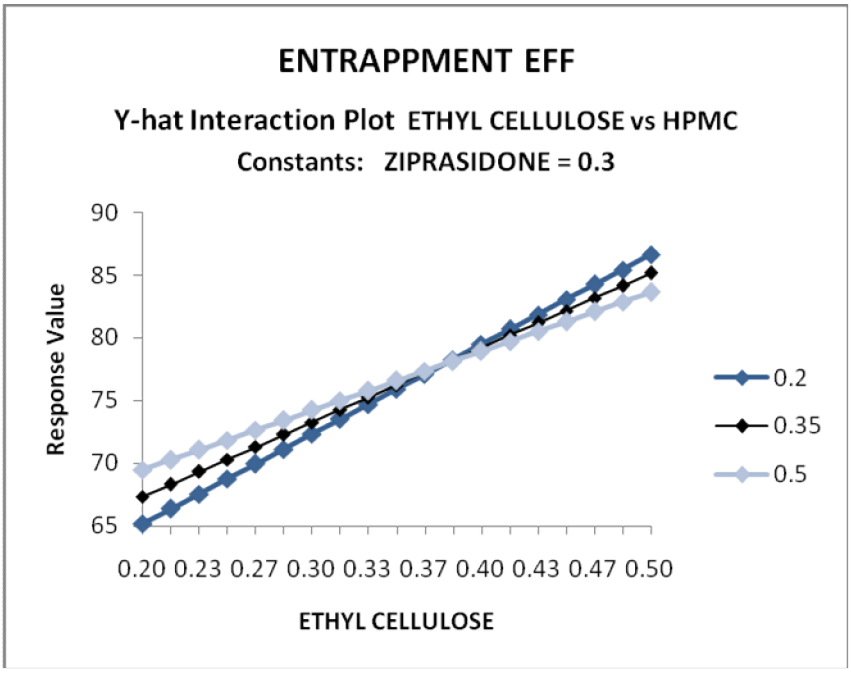

ENTRAPPMENT EFF
Y-hat Interaction Plot ZIPRASIDONE vs ETHYL
CELLULOSE
Constants: HPMC = 0.35
Response Value
90
85
80
75
70
65
60
0.10 0.14 0.19 0.23 0.28 0.32 0.37 0.41 0.46 0.50
ZIPRASIDONE
0.2
0.35
0.5

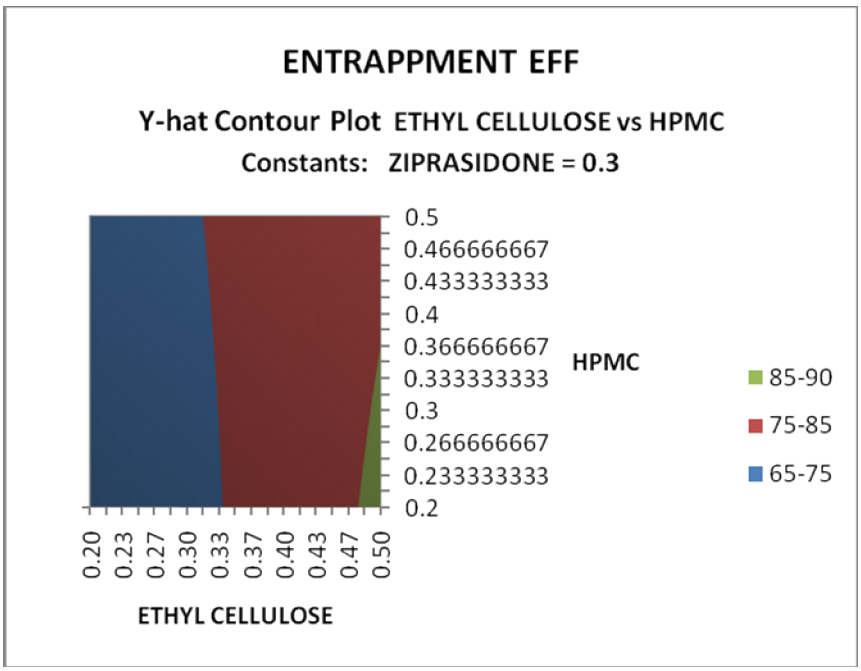

ENTRAPPMENT EFF
Y-hat Surface Plot ZIPRASIDONE vs ETHYL
CELLULOSE
Constants: HPMC = 0.35
Response Value
90
80
70
60
0.10
0.17
0.23
0.30
0.37
0.43
0.50
ZIPRASIDONE
0.2
0.366666667
ETHYL CELLULOSE
80-90
70-80
60-70

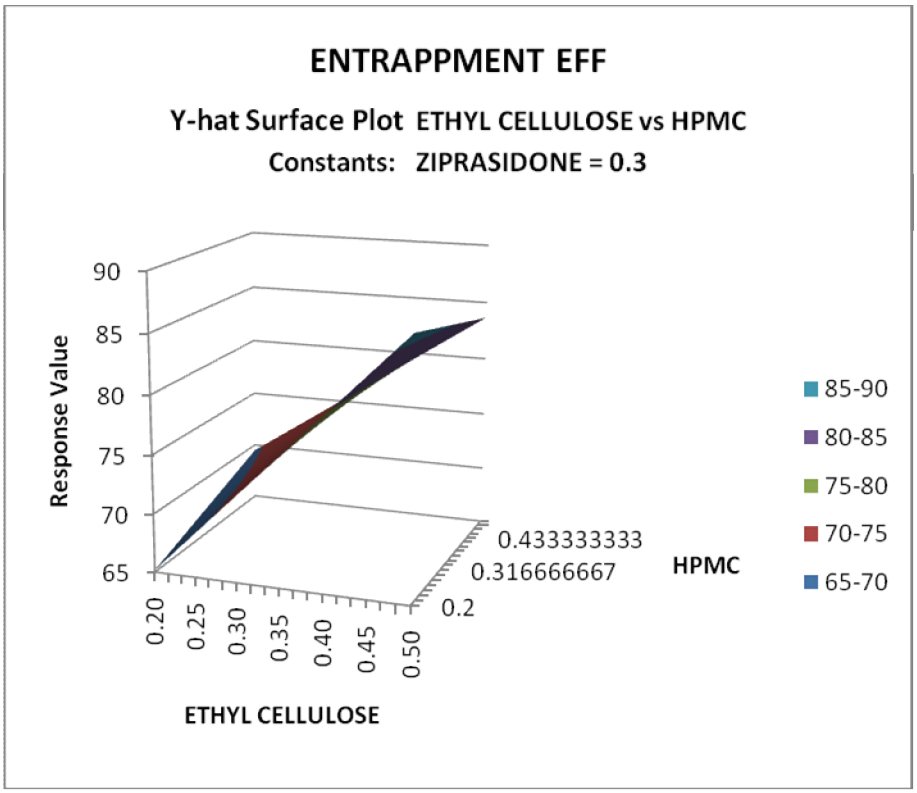

ENTRAPPMENT EFF
Y-hat Interaction Plot ZIPRASIDONE vs HPMC
Constants: ETHYL CELLULOSE = 0.35
Response Value
80
79
78
77
76
75
74
73
0.10 0.14 0.19 0.23 0.28 0.32 0.37 0.41 0.46 0.50
ZIPRASIDONE
0.2
0.35
0.5


ENTRAPPMENT EFF
Y-hat Contour Plot ZIPRASIDONE vs HPMC
Constants: ETHYL CELLULOSE = 0.35
0.5
0.466666667
0.433333333
0.4
0.366666667
0.333333333
0.3
0.266666667
0.233333333
0.2
HPMC
0.10
0.17
0.23
0.30
0.37
0.43
0.50
ZIPRASIDONE
79-80
78-79
77-78
76-77
75-76
74-75
73-74


ENTRAPPMENT EFF
Y-hat Surface Plot ZIPRASIDONE vs HPMC
Constants: ETHYL CELLULOSE = 0.35
Response Value
79
77
75
73
0.10
0.17
0.23
0.30
0.37
0.43
0.50
ZIPRASIDONE
0.2
0.366666667
HPMC
79-80
77-79
75-77
73-75


ENTRAPPMENT EFF
Y-hat Interaction Plot ETHYL CELLULOSE vs HPMC
Constants: ZIPRASIDONE = 0.3
Response Value
90
85
80
75
70
65
0.20 0.23 0.27 0.30 0.33 0.37 0.40 0.43 0.47 0.50
ETHYL CELLULOSE
0.2
0.35
0.5


ENTRAPPMENT EFF
Y-hat Contour Plot ETHYL CELLULOSE vs HPMC
Constants: ZIPRASIDONE = 0.3
0.5
0.466666667
0.433333333
0.4
0.366666667
0.333333333
0.3
0.266666667
0.233333333
0.2
HPMC
85-90
75-85
65-75
0.20
0.23
0.27
0.30
0.33
0.37
0.40
0.43
0.47
0.50
ETHYL CELLULOSE


ENTRAPPMENT EFF
Y-hat Surface Plot ETHYL CELLULOSE vs HPMC
Constants: ZIPRASIDONE = 0.3
Response Value
90
85
80
75
70
65
0.433333333
0.316666667
0.2
HPMC
85-90
80-85
75-80
70-75
65-70
0.20
0.25
0.30
0.35
0.40
0.45
0.50
ETHYL CELLULOSE

The DOE charts were obtained by feeding the entrapment efficiency data in to the DOE Pro XL software and the design space values were calculated using residual analysis.Y-hat contour plots,Y-hat surface plots,Y- hat interaction plots were plotted for independent variables that is Ziprasidone Hydrochloride,Ethyl Cellulose and Hydroxy Propyl Methyl Cellulose. The charts reveal that there is strong positive interaction between Ziprasidone Hydrochloride and Ethyl Cellulose and Hydroxy Propyl Methyl Cellulose.

By considering the below observations an optimized formula was designed, formulated and evaluated.

The Y-Contour plotsspecify the design space within which each formulation component can be varied without compromising on the entrapment efficiencies. The design space values are tabulated in Table 15

Table 15: Design Space Range for entrappment efficiency > 77% for Ziprasidone Hydrochloride

S.No	Indgredients (mg/unit)	Lower Limit	Higher Limit
1	Ziprasidone Hydrochloride	50	70
2	Ethyl Cellulose 7cps	145	150
3	HPMC 6 cps	0.4	2.0

Based on the values given in the above table an F optimum formulation was fabricated and evaluated for entrapment efficiency.Formulation composition and Entrapment efficiency achieved are given in Table 16.

Table 16: Composition and Entrapment efficiency of Optimised Formulation

S.No	Formulation No.	Formulation Ingredients	Mg/unit
1	Foptima 1	ZiprasidoneHCl	50
		EC	145
		HPMC	0.2
2	Foptima 2	ZiprasidoneHCl	60
		EC	147
		HPMC	1.0
3	Foptima 3	ZiprasidoneHCl	70
		EC	150
		HPMC	2
4		Tween 80 (ml)	1
5		IPA (ml)	
6		DCM (ml)	
7		Water (ml)	

CHARCTERSTICS	F OPTIMA-1	F OPTIMA-2	F-OPTIMA-3
YIELD(%w/w/	74.82	79.45	77.92
ASSAY(mg Ziprasidone HCl/100mg)	25.357	24.734	28.799
ENTRAPMENT EFFICIENCY	87.39	88.58	78.00

AVG.PARTICLE SIZE DISTRIBUTION (D90 ,MICRONS)	355.86	344.25	278.98

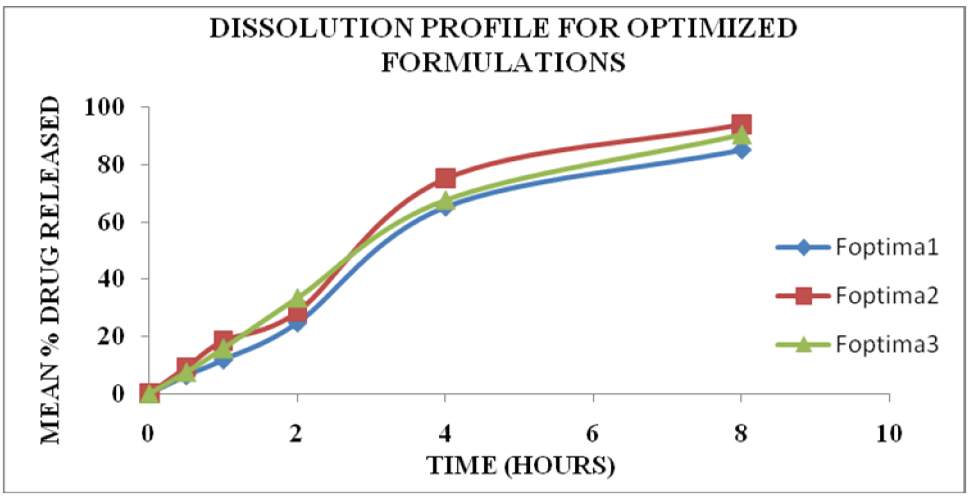
DISCUSSION:

The process used for the initial batches, is reproducible and scalable. The rsults for yield Assay, Entrappment efficeinncy and Particle size distribution are reproducible. This indicates that the selected Solvent Evaopration for Techinque is suitable formulation of Floating Microspheres.

Table17:DISOLUTION PROFILE FOR OPTIMIZED FOLUMULATION OF ZIPRASIDONE HCL MICROBALLONS

TIME	Foptima1	Foptima2	Foptima3
0	**0**	**0**	**0**
0.5	**6.35**	**9.23**	**7.54**
1	**11.87**	**18.45**	**15.88**
2	**24.79**	**28.67**	**33.49**
4	**65.32**	**75.34**	**67.7**
8	**85.29**	**94.35**	**90.58**

Figure26:DISSOLUTION PROFILE FOR OPTIMIZED FORMULATIONS



DISCUSSION:

The dissolution profile for all three formulations fabricated within the design space are showing Matching values. This indicates that any formulation fabricated within the design space will give a product having dissolution profile in a very narrow range of acceptability.

Table18:Release rate of Ziprasidone Hydrochloride from optimized formulations

Formulation	R^2				Peppas n
	Zero	First	Higuchi	Peppas	
F-optima1	0.9377	0.9843	0.9195	0.9797	0.996
F-optima2	0.9241	0.9846	0.9281	0.9746	0.874
F-optima3	0.9420	0.9946	0.9491	0.9803	0.927

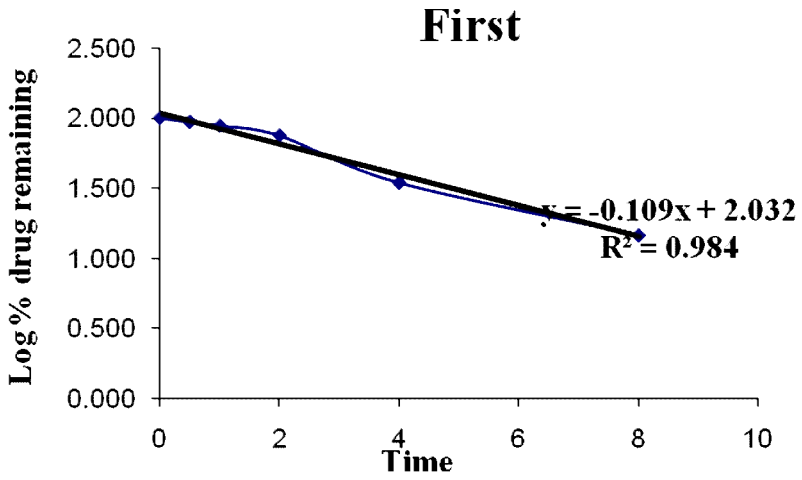


Figure 27: RELEASE RATE OF ZIPRASIDONE HCL FROM F-OPTIMA1 FORMULATION

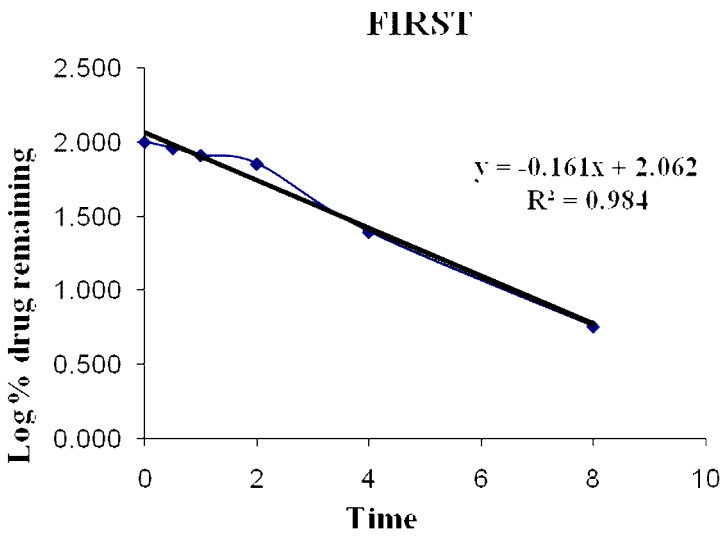


Figure28:RELEASE RATE OF ZIPRASIDONE HCL FROM F-OPTIMA2 FORMULATION

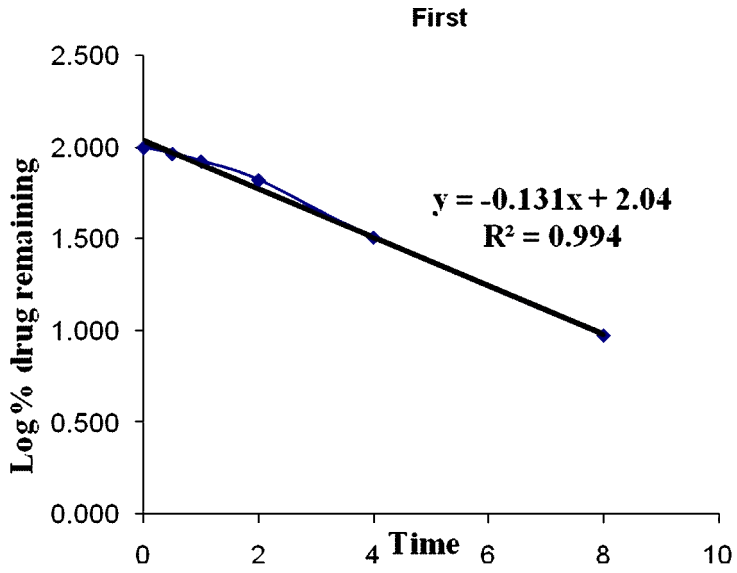


Figure29:RELEASE RATE OF ZIPRASIDONE HCL FROM F-OPTIMA3 FORMULATION

In order to understand the mechanism of drug release from the microsphers, the in vitro drug release data of the optimized formulations were fitted to Korsmeyer and Peppas release model and interpretation of release exponent values enlightens in understanding the release mechanism from the dosage form. The release

exponents thus obtained were from 0.874,0.996 and 0.927. Based on these values we can say that formulations exhibited super case

All the optimized formulations showed higher R values for first order plot indicating that the drug release followed first order kinetics and also the drug release from microspheres were by both diffusion and erosion.

ACCELERATED STABILITY STUDIES FOR ZIPRASIDONE HCL FLOATING MICROCAPSULES

Three batches of optimized formulations were fabricated as per the table 19 below:

S.no	Formulation No.	Ingredients	mg/unit	g/500 units
1	Foptima 1	ZiprasidoneHCl	50	25
		EC	145	72.5
		HPMC	0.2	0.1
2	Foptima 2	ZiprasidoneHCl	60	30
		EC	147	73.5
		HPMC	1.0	0.5
3	Foptima 3	ZiprasidoneHCl	70	35
		EC	150	75
		HPMC	2	1.0
		Tween 80 (ml)		100
		IPA (ml)		500
		DCM (ml)		500
		Water (ml)		5000

The batches were fabricated by the process described in Materials and Methods. The process was reproducible at this scale.

These batches were evaluated for Assay, % Entrapment Efficiency , Flow properties and In vitro dissolution profile in 0.1N HCL. The results of the physical

properties, Assay and% Entrapment Efficiency are given in Table. The In vitro dissolution profile for these 3 batches is given in below Table.

The Microcapsules were filled at level equivalent to 100 mg drug content in size '1' hard gelatin capsules shells, packed in 90 cc HDPE container and subjected to Accelerated Stability Studies at $4O^{0C}$/75% RH stability conditions. Samples were withdrawn at 1Month, 2Month and 3Month intervals and evaluated for assay and in vitro dissolution testing. The results are given in Table 20

Table 20:ASSAY AND IN VITRO DISSLOUTION TESTING

Tests	Specifications	F optima1			F2			F3		
		1M	2M	3M	1M	2M	3M	1M	2M	3M
Description	White to off white microcapsules filled in transperant size '1' capsules shells	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Assay (mg/100mg)	between 20 to 35 mg/100 mg	25.40	24.98	25.00	24.77	24.89	24.64	28.79	27.68	27.54
Targeted Dissolution profile										
0	0	0	0	0	0	0	0	0	0	0
0.5	NMT 10%	6.00	5.99	6.28	8,76	8.57	8.01	7.54	7.00	7.04
1.0	10 – 20%	10.97	10.00	11.43	15,88	13.09	15.54	17.28	16.43	15.98
2.0	15 – 40%	24.78	23.51	27.84	25.32	27.12	28.25	34.08	32.15	35.04
4.0	55 – 75%	63,37	60.43	65.33	70.66	73.07	71.17	72.91	70.69	71.45
8.0	NLT80% (Q)	87.98	87.09	88.96	90.42	93.22	95,24	92.83	89.09	93.65

SUMMARY AND CONCLUSION

The hydro dynamically balanced modified release dosage form of Ziprasidone Hydrochloride as targeted to be developed using a unique Microballons platform

Microballons were formulated using Ethyl Cellulose 7 cps as the controlled release polymer, Hydroxy Propyl Methyl Cellulose 6 cps as the pore former and Dichloromethane and Isopropyl alcohol as solvents for the drug and polymers. Water with 1% Tween 80 was used as the continuous phase.

The formulation was optimized by using statistically designed 2^3 Design of experiments. The Drug content, Entrapment efficiency, Particle size distribution and In vitro dissolution profile were the measurable parameters.

The formulation showed that the Drug content, Entrapment efficiency and Particle size distribution were not the dependent variable. There was no significant differences in any of the above parameters in all the 8 experimental runs

.

However, in case of the In vitro dissolution studies, the rate and extent of the release profile was strongly dependent of the drug and polymer ratio as well as on the pore former concentration.

A design space was defined within which an optimum formulation could be successfully achieved with the in vitro release profile matching to the Target product profile.

The defined design space is as per the Table 15

S. No	Formulation Ingredient	Low Level (mg/unit)	High Level (mg/ unit)
1	Ziprasidone Hydrochloride	50	70
2	Ethyl Cellulose 7 cps	145	150
3	Hydroxy Propyl Methyl Cellulose 6 cps	0.4	2.0

A formulation (F optima) was scaled up to 500 units within the design space, filled into size '1' Hard gelatin capsules, packed in 90 cc HDPE container and exposed to accelerated stability condition of 40◦C/ 75% RH. Samples were withdrawn at 1Month, 2Month and 3Month intervals and analysed for Assay and In vitro drug profiling.

The stability data does not indicate any significant change in the formulation behavior over the 3 months accelerated condition.

This formulation is selected for further scale up and process optimization.

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